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THE STEREOSELECTIVE α-ALKYLATION OF CHIRAL β-HYDROXY ESTERS AND SOME APPLICATIONS THEREOF

G. FRÄTER,* U. MÜLLER and W. GÜNTHER
Givaudan Research Company Ltd., CH-8600 Duebendorf, Switzerland

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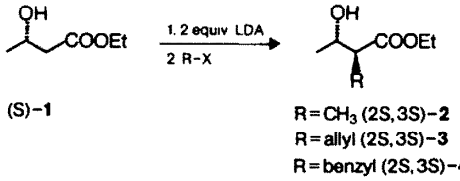
Abstract—The stereoselectivity of the α-alkylation of chiral β-hydroxy ester is discussed. The configuration of the alkylated product was proved chemically (Scheme 2). A one pot aldol-alkylation reaction was developed leading stereoselectively to racemic (*S**,*S**)-α-alkyl-β-hydroxy ester (Scheme 3, 4). Baker's yeast reduction of 2-alkyl-3-keto ester led to valuable chiral (2*RS*,3*S*)-intermediates, which were converted via the corresponding dianion to compounds with a chiral quaternary C atom (Scheme 6). Synthetic applications of the above findings are shown in the synthesis of various chiral compounds (Scheme 8 and 9).

Recently we briefly communicated on the high stereoselectivity of the α-alkylation of dianions derived from β-hydroxy ester.[1]† A large number of chiral β-hydroxy esters are available in usually high optical purity by simple reduction of the corresponding β-keto ester with (fermenting) baker's yeast (*Saccharomyces cerevisiae*).[1,3-9] Through the combination of these two findings one has a new access to a great variety of chiral compounds. To demonstrate this is the aim of this paper.

(*S*)-Ethyl-3-hydroxybutyrate ((*S*)-**1**)[4,8,9] is accessible in 50–65% chemical yield by reduction of ethyl acetoacetate. The microbiological reduction furnishes (*S*)-**1** with an enantiomeric excess (e.e.) between 70 and 97%.[8,9]

For the formation of the dianion, (*S*)-**1** was quickly added neat or in concentrated solution (THF) to two equivalents of LDA at −50°, normally at such a rate, that the temperature rose to −20° or even to 0°. In this manner the formation of the dianion is complete in minutes. The alkylating agent was normally added as a 1:2 to 1:4 (w/v) solution in HMPTA between −50° and 0° (Scheme 1). Through the use of methyl iodide, allyl bromide and benzyl bromide we isolated (2*S*,3*S*)-**2** in 67%, (2*S*,3*S*)-**3** in 75% and (2*S*,3*S*)-**4** in 82% yield. The chemical purity, i.e. the diastereoselectivity of the alkylation, as shown with GLC is in the range of 95:5 (19:1). For GLC-comparison racemic samples of the diastereomeric mixtures (*ca* 6:4) were prepared by sodium borohydride reduction of 2-methyl, 2-allyl- and -2-benzylacetoacetate, **13**, **14** and **15** respectively (see also Scheme 5). The optical purity of the respective alkylation products is only dependent on that of the starting material, which was 70% for (2*S*,3*S*)-**2** and (2*S*,3*S*)-**3**, but 85% for (2*S*,3*S*)-**4**.[10]



(S)-1

R = CH_3 (2S,3S)-2
R = allyl (2S,3S)-3
R = benzyl (2S,3S)-4

Scheme 1.

The major problem concerned the rigorous proof of the stereochemistry of the products. Although ^{1}H-NMR especially J(2,3)- gave good indication for the (2*S*,3*S*)-stereochemistry[11,12] in the case of **2** (J(2,3) = 7.3 Hz in our main alkylation product and ~4 Hz in the side product), with **3** and **4** assignment was ambiguous. J(2,3) is 5.15 Hz in (2*S*,3*S*)-**3** and 4.78 Hz in (2*R*,3*S*)-**3** and it is 4.4 Hz in both diastereomers of **4**. Because of that we decided to prove the stereochemistry chemically and at the same time demonstrate a further useful preparative consequence of the stereoselectivity of the alkylation (Scheme 2).

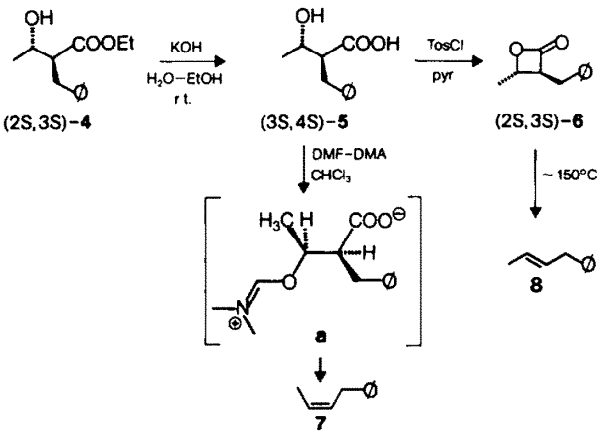
(2*S*,3*S*)-**4** was hydrolyzed in over 85% yield to (2*S*,3*S*)-**5** with KOH in water ethanol at room temperature without any epimerization on C(2). The crystalline product was further converted without recrystallization to the β-lactone (3*S*,4*S*)-**6** by treating it with TosCl in pyridine (82%). J(3,4) in (3*S*,3*S*)-**6** was found to be 4.4 Hz, which according to the literature[13,14] was indicative for the *trans* geometry. More conclusive was the pyrolysis[13,14] of **6**, which furnished *trans*-4-phenyl-2-butene (**8**) in 84% yield and over 98% chemical purity.

On the other hand treatment of (2*S*,3*S*)-**5** with dimethylformamide dimethyl acetal[15,16] (DMF–DMA) in chloroform at 60° yielded after careful work-up *cis*-4-phenyl-2-butene (**7**) in 87% yield and 97% chemical purity. The mechanism of the above decarboxylative-dehydration has been elucidated[16] as a stereocontrolled anti-elimination, in our case going through a zwitterion **a**.

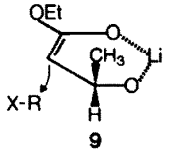
The combined results of the pyrolysis of the β-lactone **6** to *trans*-4-phenyl-2-butene on the one hand and the decarboxylative-dehydration of **5** to *cis*-4-phenyl-2-butene on the other hand[17] unambiguously proved the stereochemistry of **5** and consequently that of **4** as being (2*S*,3*S*). Based on the results the steric course of alkylation can superficially be depicted as in **9**.

The alkylation thus yields a *l*-product by a *lk*-

†See also Ref. 2.



Scheme 2.



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mechanism.[18] This was already put forward by Kraus *et al.*[19] for their case of dianion oxidation. The schematic picture **9** will only show that the reason for this case of "acylic stereoselection"[20] is a rigid cyclic structure due to the chelation of a Li cation through the two O-anions.[21] This allows a stereoselection with a $\Delta\Delta G^{\ddagger}$ of 1.4–1.5 kcal/mol (at $-20°$).

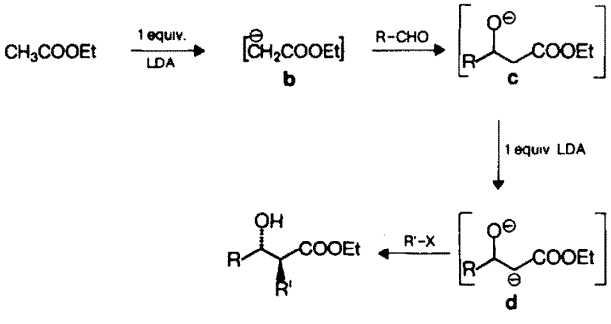
It is notable that the enantiomeric compounds, i.e. (2*R*,3*R*)-**2**, **3** and **4** are also accessible by starting with ethyl (*R*)-3-hydroxybutyrate. The latter is available either by depolymerization of poly-(*R*)-3-hydroxybutyrate[22] or by microbiological reduction of ethyl acetoacetate by *Geotrichum candidum*.[9] Indeed Pfander *et al.*[23] prepared (*R*)- and (*S*)-Lavandulol by using methyl (*R*)- and (*S*)-3-hydroxybutyrate for the key alkylation step with 3-methyl-2-butenyl bromide.

In the course of the chemical deduction of the stereochemistry of (2*S*,3*S*)-**4** (Scheme 2) it was simultaneously shown, that the stereoselectivity in the alkylation step is also the prerequisite for the preparation of pure geometric isomers of olefins (see Ref. 13). Obviously, if the olefins are the desired end products, one does not need chiral educts and is satisfied with the even more easily available β-hydroxy ester.[17,24]

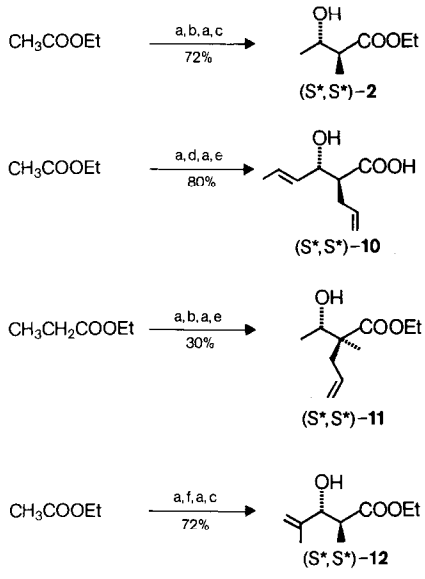
With this in mind, we thought that the primary intermediate of an aldol reaction, the monoanion of a β-hydroxy ester could be used *in situ* for a stereoselective alkylation, by adding another equivalent of LDA to form a dianion. The one-pot aldol-alkylation reaction would proceed through three anionic species→**b**→**c**→**d** as shown in Scheme 3.

The above idea was carried out with good results (Scheme 4). First (*S**,*S**)-**2** was synthesized by successive addition of one equivalent of LDA, acetaldehyde, again one equivalent of LDA and finally of methyl iodide to ethyl acetate. (*S**,*S**)-**2** could be isolated in 72% yield, the only impurity found was 5% of (*R**,*S**).**2**. In an analogous sequence of reactions (*S**,*S**)-**10** was prepared in 80% yield. Assignment of the stereochemistry of (*S**,*S**)-**10** is mainly based on analogy, beside J(2,3) of *ca* 6 Hz, which is quite large in this series.[12] The diastereoselectivity in this case amounted to *ca* 93:7. In the next example ethyl propionate was taken as a starting material aiming for a quaternary C atom (*vide infra*). When the reaction was quenched with water after the aldol reaction, only a *ca* 1:1 mixture of (*S**,*S**)- and (*R**,*S**)-**2** was isolated, showing a complete lack of stereoselectivity.

Treatment of the intermediate monoanion with one equiv LDA and then with MeI furnished (*S**,*S**)-**11**



Scheme 3.



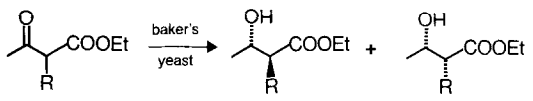
a) one equiv. LDA b) CH_3CHO c) CH_3I
d) trans–CH_3CH=CH–CHO e) CH_2=CH–CH_2Br
f) CH_2=CH(CH_3)–CHO

Scheme 4.

in low yield (30%) but in high selectivity (~96:4) (*vide infra*). In the last example of Scheme 4 first ethyl acetate was reacted with methacrolein and then through the dianion the intermediate was methylated to (*S*,S**)-**12** in high yield (72%) and the usual selectivity of *ca* 95:5. In (*S*,S**)-**12** J(2,3) is 8 Hz. This compound is an interesting one in so far as it is set up for hydroboration.[25]

It is well known that hydride reduction of ethyl 2-alkylacetates, i.e. of **12**, **13** and **14**, leads to a nearly 1:1 mixture of the two racemic diasteromers, though with $Zn(BH_4)_2$ a selectivity in favour of the (2*R**,3*S**)-isomer was observed in certain cases.[26] Now that we had access to the (*S,S*)-isomers (see above, Scheme 1) in 95% chemical and 70% (**2** and **3**) or 85% (**4**) optical yield it was of interest to learn, which—if any—are the products of yeast reduction of the racemic and enolizable compounds **13**, **14** and **15**. The only precedents in literature for yeast reduction of this type of compounds, where two chiral centers could result, are the cyclic analogues, ethyl 2-oxo-cyclohexanecarboxylate[4,5] and ethyl 2-oxocyclopentanecarboxylate,[4] which yielded ethyl (1*R*,2*S*)-2-hydroxycyclohexancarboxylate and -cyclopentanecarboxylate, respectively, in good chemical and optical yield.[27]

Baker's yeast reduction of **13**[1,28,29] (Scheme 5) yielded a 1:3 mixture of (2*S*,3*S*)-**2** and (2*R*,3*S*(-**2** in 65% yield. The two isomers were not separated in this case. Comparison with the alkylation product (2*S*,3*S*)-**2** (Scheme 1) made a sound analysis of the ^1H NMR spectrum of the mixture possible (Experimental). For the assignment of the absolute configuration of the two isomers there is good circumstantial evidence as will be seen later (Scheme 6). It is important to state here, though also based on later evidence, that the optical purity on C(3) of the mixture is nearly 100%. That means that it is substantially higher than the one usually achieved at the preparation of (*S*)-**1**.[4,8,9]



R=CH_3 **13** (2S,3S)-**2** 1:3 (2R,3S)-**2**
R=allyl **14** (2S,3S)-**3** 3:1 (2R,3S)-**3**
R=benzyl **15** (2S,3S)-**4** 2:1 (2R,3S)-**4**

Scheme 5.

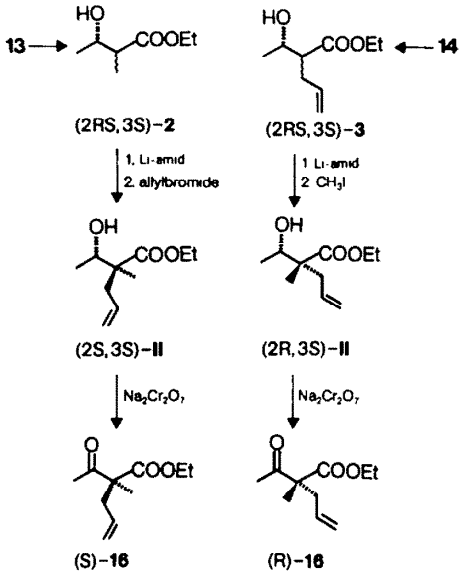
Analogous reduction of **14** gave a *ca* 3:1 mixture of (2*S*,3*S*)-**3** and (2*R*,3*S*)-**3**, respectively. The two isomers were separated in this case by means of preparative GLC. The main product of the reduction was identical with the alkylation product in Scheme 1 except for the higher $[\alpha]_D^{22}$-value, which was +14.5° in this case, as compared to 9.7° (~70% e.e.) in the other. This means that (2*S*,3*S*)-**2** prepared through direct reduction of **14** is nearly 100% e.e. The side product with $[\alpha]_D^{22} = +5.8$ must be (2*R*,3*S*)-**3**; ^1H NMR shows that it is a (2*R**,3*S**)-isomer of **3** and evidence based on the results in Scheme 6 shows that it is not (2*S*,3*R*)-**3**.

The third baker's yeast reduction of a 2-alkylacetoacetate, that of **15**, gave only a 22% yield of a 2:1 mixture of (2*S*,3*S*)-**4** and (2*R*,3*S*)-**4**, besides 45% of the educt.[29] Preparative GLC separation furnished optically pure (2*S*,3*S*)-**4** with $[\alpha]_D^{22} = -35.85°$ in good agreement with $[\alpha]_D^{22} = -30.7°$ of the alkylation product (Scheme 1), which is supposed to be of ~85% optical purity (Experimental). The side product, to which we assign the (2*R*,3*S*) absolute configuration in analogy to the above examples, had $[\alpha]_D^{22} = +35.4°$ but also 7% of (2*S*,3*S*)-**4** as an impurity. This corrects the rotatory power of (2*R*,3*S*)-**4** to$[\alpha]_D^{22} = +40.8°$.

The above described baker's yeast reductions are seemingly substrate nonenantiospecific and highly product enantiospecific.[30]

Having succeeded to reduce **13** and **14** to (2*RS*,3*S*)-**2** and (2*RS*,3*S*)-**3** respectively in good chemical and concerning C(3) in very high optical yield, two things were gained at the same time. Firstly for the preparation of a chiral quaternary C atom through a dianion alkylation one alkyl group is already introduced, the stereochemistry at C(2) being of no importance. Secondly the optical purity of the directing chiral moiety is nearly 100% compared to 70–85% in *S*-(**1**). These considerations are demonstrated in Scheme 6.

Allylation of (2*RS*,3*S*)-**2** gave (2*S*,3*S*)-**11** in 57% yield. The diastereoselectivity of this alkylation was 94:6. On the other hand (2*RS*,3*S*)-**3** could be methylated in 56% yield with a selectivity of 96:4, which was improved to 98:2 through chromatography. Both yields were higher than described before[1] by the use of lithiumcyclohexylisopropylamide instead of LDA.[28] (2*S*,3*S*)-**11** was oxidized in 81% yield to (*S*)-**16** with $[\alpha]_D^{22} = -27.05°$ (e.e. ~91%) and similarly (2*R*,3*S*)-**11** to (*R*)-**16** with $[\alpha]_D^{22} = +28.5°$ (e.e. ~96%). The optical purity of (*S*)- and (*R*)-**16** can directly be seen by the use of chiral shift reagent ($Eu(hfc)_3$) as the acetyl group splits up in two singlets in the ratio of ~96:4 for (*S*)-**16** and of ~98:2 for (*R*)-**16** respectively. This proves the nearly 100% e.e.



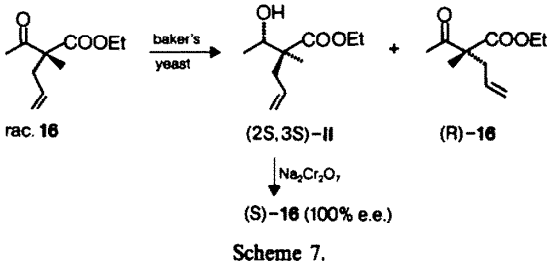
Scheme 6.

of C(3) in the yeast reduction products of **13** and **14**, as the only "optical pollution" was brought in through the 5% and 2% failure in the diastereoselectivity of the alkylation. It also proves the absolute configuration of (2*R*,3*S*)-**2** and (2*R*,3*S*)-**3** for which we had no authentic materials from the alkylation reactions (Scheme 1) and which could have had the (2*S*,3*R*)-configuration.

Interestingly, reduction of *rac*-**16** with baker's yeast is an educt- and product-enantioselective reaction[7] (Scheme 7). The enzymatic reduction furnished (2*S*,3*S*)-**11** in 20% yield and virtually 100% chemical and optical purity. The other product of the reaction was the optically slightly enriched (*R*)-**16** with $[\alpha]_D^{22} = +8.1°$ (e.e. 27.5%).[31] Finally oxidation of this sample of (2*S*,3*S*)-**11** ($[\alpha]_D^{22} = +7.8°$) yielded (*S*)-**16** in optically pure form ($[\alpha]_D^{22} = -29.6°$).

The above described (Scheme 6) straightforward sequence of reactions for the preparation of a quaternary chiral C atom in a molecule with two or more functional groups seemed interesting enough for further evaluation.

In Scheme 8 an application is shown,[32] where an electrophile with a masked CO group (Wichterle's reagent[33]) was used in the alkylation of (2*RS*,3*S*)-**2**. (*S*,*S*)-**17** was isolated in 53% yield. The stereoselectivity in this step is difficult to be seen, because of the additional *E*/*Z*-isomers in the side chain. But it must have been in the range of ~93:7, as optishift experiments with (*S*)-**19** revealed an optical purity for

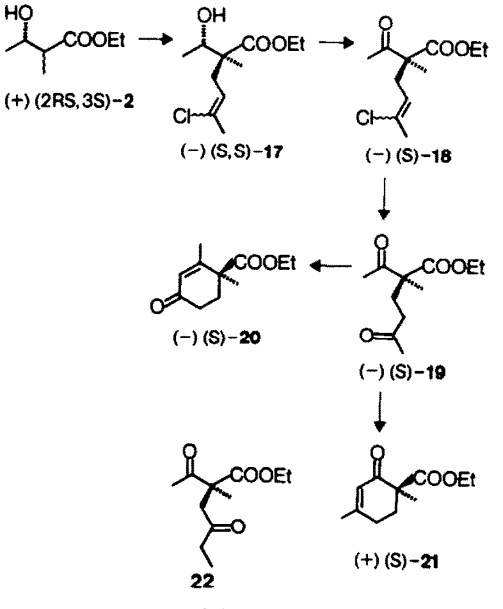


Scheme 7.

that compound of *ca* 85%. (*S*,*S*)-**17** was oxidized with sodium bichromate in high yield (87%) to (*S*)-**18** ($[\alpha]_D^{22} = -27.8°$), which was treated with $Hg(OCOCF_3)_2$ in nitromethane.[34] (*S*)-**19** ($[\alpha]_D^{22} = -8.3°$) was isolated in 60% yield, beside small amounts of already cyclized product (*S*)-**21** and of one, which is probably **22** (see Ref. 34). As mentioned already optishift experiments with (*S*)-**19** were successful. The singlets at 2.16 and 2.14 ppm splitted into two singlets each upon treatment with $Eu(hfc)_3$ in $CDCl_3$ (400 MHz) in a ratio of *ca* 93:7. The next problem was to achieve a regioselective aldol condensation to (*S*)-**20** and to (*S*)-**21**. Terashima *et al.*[35] studied a similar problem with 3-acetyl-3-methyl-2,6-heptadione and found that the acid catalyzed reaction led to type-**20** products in nonpolar solvents and to type-**21** products in polar solvents. Kreiser *et al.*[36] successfully cyclized rac **19** either to rac **20** or to rac **21** with high regioselectivity. We succeeded in regiospecifically transforming (*S*)-**19** into (*S*)-**20** in nearly quantitative yield by using pyrrolidine–acetic acid in ether.[35] Optishift experiments with (*S*)-**20** confirmed the measurements with (*S*)-**19**, the triplet at 1.28 ppm splitting up into two triplets in a ratio of *ca* 94:6. On the other hand treatment of (*S*)-**19** in toluene at reflux with catalytic amounts of TosOH furnished a 4:1 mixture of (*S*)-**21** and (*S*)-**20**.

As a last example the synthesis of a chiral cyclobutanone and of a chiral oxetane, respectively, shall be described. Chiral cyclobutanones are scarce in the literature. One interesting new method is the optical resolution of certain rac cyclobutanones.[37] (+)(*R*) and (−)(*S*)-2-methylcyclobutanone have been prepared only recently with 64% and 62% e.e., respectively.[38] We were interested in chiral cyclobutanones because of our work on the optical induction in the course of the [2 + 2]-cycloaddition of chiral ketones[39] and also in connection with the so-called homo-Favorskii rearrangement.[39,40]

Alkylation of (2*RS*,3*S*)-**2** with crotyl bromide



Scheme 8.

(~80% *E*, ~20% *Z*) yielded (*s,s*)-**23** in 60% yield and the usual ~95:5 diastereoselectivity (GLC, ^{1}H NMR). Reduction with $LiAlH_4$ to (2*R*,3*S*)-**24** and protection of the primary alcohol function by dimethyl-t-butylsilyl chloride gave (2*R*,3*S*)-**25** in 72% yield ($[\alpha]_D^{22} = +1.18°$). Oxidation to (*R*)-**26** and deprotection furnished (*R*)-**27** ($[\alpha]_D^{22} = +16.6°$), which was converted into the tosylate (*R*)-**28** ($[\alpha]_D^{22} = +2.04°$; ~30% overall yield from (2*RS*,3*S*)-**2**). Optishift experiments with (*R*)-**26** showed a *ca* 94:6 ratio of two singlets for the acetyl group originally at 2.13 ppm, indicating a ~88% e.e. for the compounds in Scheme 9.

Treatment of (*R*)-**28** with potassium t-butylate in t-BuOH (conf. Ref. 41) furnished a *ca* 3:4 mixture of (*S*)-**29** and (*R*)-**30** in 77% yield. The products were easily separated on a silica gel column, (*R*)-**30** being eluted first. (*S*)-**29** displayed a characteristic band in the IR at 1780 cm^{-1}, $[\alpha]_D^{22} = -103°$ and an intensive CD-band with $\Delta\epsilon$ (360 nm) = 1.56, which also confirms the absolute configuration (see Ref. 38). (*R*)-**30**, $[\alpha]_D^{22} = +76.3°$, showed no CD, obviously it is too far in the UV. The exomethylene protons appear in the NMR spectrum at 4.43 and 4.39 ppm with J ~ 5.5 Hz, the ring protons next to the oxygen at 4.02 and 3.68 ppm with J ~ 4 Hz.[42]

EXPERIMENTAL

The [α]-values were measured, if not otherwise stated, in $CHCl_3$ on a Perkin–Elmer 141 Polarimeter. NMR spectra were obtained on a Bruker WH360 or 400 or a Varia XL-100-12 Spectrometer in $CDCl_3$. Shifts are reported as ppm relative to TMS. For GLC a C. Erba Fractovap D (FID) was used with different 3 m packed columns.

Abbreviations: m = multiplet; s = singlet; d = doublet; d × m = doublet of multiplets.

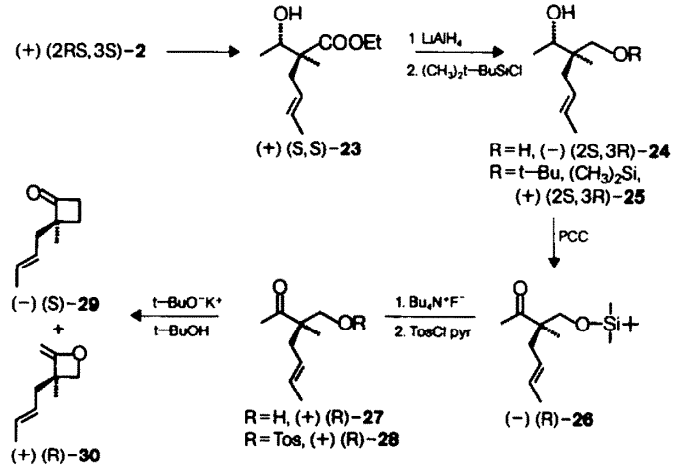
Ethyl (2S,3S)-3-*hydroxy*-2-*methyl-butyrate* (2S,3S)-**2**. To the soln of 44.4 g (0.44 mole) diisopropylamine in 100 ml anhyd THF 275 ml of a 1.6 M soln of MeLi in ether were added at 0–10°. The soln of lithium diisopropylamide was cooled to −50° and 26.4 g (0.2 mole) of ethyl (3*S*)-3-hydroxybutyrate ($[\alpha]_D^{22}$ ($CHCl_3$, *c* = 0.95) = 30.5°, e.e. ~70%) was added within 10 min, keeping the temp between −50° and −20°. To the dianion the soln of 42.6 g MeI in 50 ml HMPTA was added, the temp of which rose to 0°. After stirring 10 min the mixture was poured on ice water and extracted with ether. The ether phase was dried on $MgSO_4$ and evaporated. The product was distilled at 77–78° and 10 mm Hg, giving 19.8 g (67.8%) (2*S*,3*S*)-**2**. GLC (XE-60) showed a selectivity of 95.5% (2*S*,3*S*)-**2** to 4.5% (2*R*,3*S*)-**2**. $[\alpha]_D^{22}$ (*c* = 1.3) = +19.1°. NMR (360 MHz): δ 4.17 (q, $-OCH_2-$), 3.92–3.83 (d × q, after adding D_2O J(2,3) = 7.35 Hz; H–C(3)), 2.71 (d, OH), 2.5–2.4 (d × q, J(2,3) = 7.35 Hz; H–C(2)), 1.28 (t, $\underline{CH_3}-CH_2-$), 1.22 and 1.19 (d–s) ppm. (Found: C, 57.34; H, 9.92. Calc for $C_7H_{14}O_3$ (146.19): C, 57.51; H, 9.65%).

Ethyl (2S,3S)-2-*allyl*-3-*hydroxybutyrate* ((2S,3S)-**3**). To 0.1 mole of LDA in 30 ml THF and 70 ml ether at −50° 5.5 g (41.5 mmole) of ethyl (*S*)-3-hydroxybutyrate ($[\alpha]_D^{22}$ ($CHCl_3$, *c* = 0.95) = 30.5°, e.e. ~70%) was added in one dash letting the temp rise to 0°. The mixture was stirred at this temp for 2 min and then 5.4 g (45 mmole) allyl bromide in 20 ml HMPTA was added quickly. The temp rose to 25° and after the addition in 12 min to 38°. After ½ hr it was back to room temp and the reaction was worked up with water, $2NH_2SO_4$ and ether. The crude product (7.1 g) was chromatographed on silica gel with hexane ether (1:1) furnishing 5.4 g (75.5%) of a 95:5 mixture (GLC, XE-60) of (2*S*,3*S*)-**3** and (2*R*,3*S*)-**3**. B.p. 85° at 10 mm Hg. $[\alpha]_D^{22}$ (*c* = 1.1) = +9.7°; e.e. ~70%, compared to the optically pure isomer. NMR (360 MHz) was identical with the optically pure compound isolated with prep. GLC (*vide infra*).

Ethyl (2S,3S)-2-*benzyl*-3-*hydroxybutyrate* (2S,3S)-**4**). Analogously to the methylation ethyl (3*S*)-3-hydroxybutyrate ($[\alpha]_D^{22}$ (*c* = 1.41) = +33.58°; e.e. ~85%) was benzylated in 82.2% yield with a selectivity of 97:3. B.p. 102–103° at 0.15 mm; $[\alpha]_D^{22}$ (*c* = 1.3) = −30.7°; e.e. ~85%. NMR (100 MHz): δ 7.35–7.15 (5 aromatic protons), 4.1 (q, $-O-CH_2$), 4.0–3.75 (after addition of D_2O, d × q, J(2,3) = 4.4 Hz) H–C(3)), 3.05–2.9 (m, $-CH_2-Ar$), 2.8–2.55 (m, H–C(2)), 1.26 (d, 3H–C(4)), 1.15 (t, $-CH_2-\underline{CH_3}$) ppm. (Found: C, 69.96; H, 8.31. Calc. for $C_{13}H_{18}O_3$ (222.28): C, 70.24; H, 8.16%.)

(2S,3S)-2-*Benzyl*-3-*hydroxy-butyric acid* ((2S,3S)-**5**). 15 g (2*S*,3*S*)-**4** (67 mmole) was stirred at room temp in the soln of 16.8 g KOH in 150 ml water–EtOH (1:1) for 2 hr. Work up yielded 11.2 g of (2*S*,3*S*)-**5** with a m.p. 123.5–125°. $[\alpha]_D^{22}$ (*c* = 1.18) = −26°; e.e. ≥ 85%. NMR (360 MHz): δ 7.34–7.20 (m, 5 aromatic protons), 3.45–3.38 (m, H–C(3)), 3.05–2.96 (m, CH_2-Ar), 2.76–2.7 (m, H–C(2)), 1.31 (d, 3H–C(4)) ppm, very broad OH-signal between 2.6 and 1.5 ppm. (Found: C, 67.90; H, 7.17. Calc for $C_{11}H_{14}O_3$ (194.23): C, 68.02; H, 7.27%.)

(3S,4S)-3-*Benzyl*-4-*methyl*-2-*oxetanone* (**6**). 3.88 g (20 mmole) (2*S*,3*S*)-**5** was dissolved in 100 ml pyridine. At −5°–0° 11.4 g (60 mmole) tosylchloride was added and the mixture was set aside overnight in the refrigerator (3°). The following morning the reddish-brown soln was poured on



Scheme 9.

ice and worked up with $2NH_2SO_4$, sat $NaHCO_3$aq and ether. The crude product (3.4 g) was distilled at 95–100° and 0.03 mm (Kugelrohr) to give 2.9 g (82%) of **6**. $[\alpha]_D^{22}$ ($c = 1.7$) = + 21.4°. CD (acetonitrile): $\Delta\epsilon$ (218 nm) = + 3.7. IR (film): 1820 cm^{-1}. NMR (360 MHz): δ 7.36–7.16 (m, 5 aromatic H), 4.5–4.43 (d × q, J(3,4) = 4.2 Hz, H–C(4)), 3.51–3.45 (m, H–C(3)), 3.2–3.0 (ABX pattern of $-CH_2-$ Ar), 1.45 (d, CH_3–C(4)) ppm. (Found: C, 74.87; H, 6.74. Calc. for $C_{11}H_{22}O_2$ (176.22): C, 74.98; H, 6.86%.)

cis-4-*Phenyl*-2-*butene* (**7**). 7.7 g (2*S*,3*S*)-**5** (40 mmole) was suspended in 100 ml $CHCl_3$ and to this suspension 22.4 g (0.19 mole) dimethylformamide dimethyl acetal was added. The clear soln was heated at reflux for 60 min. The $CHCl_3$ was distilled off through a Vigreux column, the residue was taken up in pentane and washed with water. Finally the crude produce (6 g) was chromatographed on silica gel with pentane. Pentane was distilled off through a column and the product was distilled at 75° and 10 mm Hg (Kugelrohr): 4.6 g (87%) of **7**. GLC showed *ca* 3% of **8** as the only impurity.

trans-4-*Phenyl*-2-*butene* (**8**). 1.76 g (10 mmole) **6** was heated neat at 150–160°. **8** was continuously distilled off. Yield: 1.1 g (84.6%) **8**. GLC (XF 1155) and NMR showed no traces of *cis*-4-phenyl-2-butene (**7**).

One-pot aldol-alkylation reactions. (S*,S*)-**2**: 8.8 g (0.1 mole) EtOAc was added to 100 ml of 2N LDA-soln (ether–THF ~ 1:1) at −60°. The temp rose to −30°. The mixture was cooled to −50° again and 4.5 g (0.1 mole) acetaldehyde was added within 5 min. The temp rose to −15°. After cooling to −50° again 1.1 equiv LDA was added as a 1N soln in THF–ether not allowing the temp to rise above −20°. After the addition was complete 10 ml MeI in 25 ml HMPTA was quickly added at −20° allowing the temp to rise to 35°. It was stirred for another 10 min and then worked up with $2NH_2SO_4$ and ether. The crude yield was 15 g. Distillation (Kugelrohr) at 80–85° and 10 mm Hg furnished 10.6 g (72.5%) of the product. GLC showed a diastereoselectivity of 95:5. NMR was identical with that of (2*S*,3*S*)-**2**.

Ethyl (S*,S*)-2-*allyl*-3-*hydroxy*-4-*hexenoate* ((S*,S*)-**10**. Exactly analogously to the preparation of (*S**,*S**)-**2**, (*S**,*S**)-**10** was prepared in 80% yield out of EtOAc, crotonaldehyde and allyl bromide. A 0.1 mole experiment yielded 16 g of the title compound; b.p.100–105° at 0.07 mm Hg. GLC on different packed columns did not reveal any impurity. NMR (360 MHz) only showed a *ca* 7% impurity as a t(CH_3CH_2O), which could belong to the (*R**,*S**)-isomer. NMR (360 MHz): δ 5.8–5.18 (m, H–C(4), H–C(5)), 5.5–5.43 (m, H–C(2')), 5.11–5.0 (m, 2H–C(3')), 4.21–4.12 (m, $-O-CH_2-$, H–C(3)), 2.56–2.50 (after addition of D_2O d × t, J(2,3) ~ 6 Hz, H–C(2)), 2.39–2.3 (m, 2H–C(1')), 1.71 (d × m, 3H–C(6)), 1.26 (t, CH_3-CH_2-) ppm. (Found: C, 66.45; H, 9.34. Calc. for $C_{11}H_{18}O_3$ (198.26): C, 66.64; H, 9.15%.)

Ethyl (S*,S*) - 2 - *allyl*,2 - *methyl*,3 - *hydroxybutyrate* ((S*,S*)-**11**). Analogously to the preparation of (*S**,*S**)-**2**, (*S**,*S**)-**11** was prepared out of ethyl propionate, acetaldehyde and allyl bromide. A 0.1 mole experiment yielded 12 g of crude product (theory 18.6 g), which was chromatographed on silica gel with hexane ether (1:1). First 5 g of impurities were eluted, then 5.6 g (30%) of the product. B.P. (Kugelrohr): 55–60° at 0.15 mm Hg. GLC (XE-60) comparison with (2*R*,3*S*)-**11** showed that the selectivity of the alkylation was 94:6. NMR (360 MHz) was identical with that of (2*S*,3*S*)-**11** (*vide infra*).

Ethyl (S*,S*) - 2,4 - *dimethyl* - 3 - *hydroxy* - 4 - *hexenoate* ((S*,S*)-**12**). Analogously to the above examples 0.1 mole EtOAc was first reacted with methacrolein, the intermediate converted to the dianion and alkylated with MeI. Work up yielded 15 g of crude oil, which was distilled at 65–68° and 0.05 mm Hg to give 11.2 g (65%) of (*S**,*S**)-**12**. NMR (400 MHz): δ 4.99–4.97 and 4.95–4.93 (m-s, two vinyl protons), 4.22–4.13 (m, $-O-CH_2-$, H–C(3)), 4.14 (after addition of D_2O, d, J(3,2) ≈ 8 Hz; H–C(3)), 2.73 (d, J ~ 5 Hz, OH), 2.66 (d × q, J(2,3) ≈ J(2,CH_3 ~ 8 Hz; H–C(2)), 1.74 (broad s, CH_3–C(4)), 1.28 (t, CH_3-CH_2-), 1.12 (d, CH_3–C(2)) ppm. (Found: C, 62.49; H, 9.51. Calc for $C_9H_{16}O_3$ (172.22): C, 62.76; H, 9.36%).

Reduction of 2-substituted ethyl acetoacetates by baker's yeast. *Reduction of ethyl* 2-*methylacetoacetate* (**13**) *to ethyl* (2RS,3S)-2-*methyl*-3-*hydroxybutyrate* ((2RS,3S)-**2**). 100 g baker's yeast (*Saccharomyces cerevisiae*, Klipfel AG, CH-Rheinfelden) and 150 g of saccharose were mixed in 1:1 of tapwater in a 1.5l 3-necked round bottom flask. After ½ hr 10 g of **13** was added to the fermenting broth and the mixture was stirred for 24 hr. At this point 50 g of sugar was added and stirring was continued for another 24 hr. After addition of 50 g Hyflow the mixture was filtered through a sintered glass funnel (G3), the filtrate was extracted with ether. This is sometimes a lengthy procedure because of emulsions. Extraction was repeated at least four times. The ether phase was dried over Na_2SO_4 and the solvent was distilled off through a Vigreux column. After chromatography on silica gel with pentane–ether (1:1) 5.5 g of a mixture of products was isolated, besides 1 g (10%) of educt.

The mixture consisted of 75% of (2*R*,3*S*)-**2** and 25% (2*S*,3*S*)-**2** (GLC, NMR). The ratio varied slightly, possibly because of some discrimination during the work up of the emulsion. $[\alpha]_D^{22}$ ($c = 1.0$) = 9.1°. NMR (400 MHz): δ 4.21–4.15 (2q ~ 1:3,–O–CH_2–), 4.1–4.04 (m, H–C(3) of (2*R*,2*S*)-**2**), 3.92–3.83 (m, H–C(3) of (2*S*,3*S*)-**2**), 2.73–2.67 (OH of (2*S*,3*S*)-**2**), 2.63–2.56 (OH of (2*R*,3*S*)-**2**), 2.5 (d × q, H–C(2) of (2*R*,3*S*)-**2**, J(2,3) ~ 4 Hz), 2.44 (d × q, H–C(2) of (2*S*,3*S*)-**2**, J(2,3) = 7.3 Hz), 1.28 (t, CH_2-CH_3), 1.2 (d, CH_3– of (2*S*,3*S*)-**2**, 1.195 and 1.19 (2d, Me-groups of (2*R*,2*S*)-**2** ppm.

Reduction of ethyl 2-*allylacetoacetate* (**14**) *to ethyl* (2RS,3S)-2-*allyl*-3-*hydroxybutyrate* ((2RS,3S)-**3**). 10 g **14** was reduced with baker's yeast as described above. The crude product (14 g) was flash-chromatographed on silica gel with hexane–ether (8:2) to yield 0.7 g (7%) of the starting material and 8.4 g (84%) of a mixture consisting of 75% (2*S*,3*S*)-**3** and 25% (2*R*,3*S*)-**3**. B.p. 85° at 10 mm Hg. $[\alpha]_D^{22}$ ($c = 1.04$) = + 12.5°.

(Found: C, 62.55; H, 9.42. Calc for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36%.)

The above mixture was separated with preparative GLC (Carbowax). The (2*S*,3*S*)-isomer was eluted first.

Ethyl (2S,3S)-2-*allyl*-3-*hydroxybutyrate* ((2S,3S)-**3**). $[\alpha]_D^{22}$ ($c = 0.38$) = + 14.5°; e.e. ~ 100%. NMR (360 MHz): δ 5.81–5.7 (m, 1 vinyl proton), 5.13–5.01 (m, $=CH_2$), 4.18 (q, $-O-CH_2-$), 3.93 (after addition of D_2O d × q, J(2,3) = 5.15 Hz, H–C(3)), 2.51 (d, J(OH, 3) = 7 Hz, OH), 2.5–2.39 (m, H–C(2) and 2H–C(1')), 1.27 (t, $-OCH_2CH_3$), 1.24 (d, 3H–C(4)) ppm.

Ethyl (2R,3S)-2-*allyl*-3-*hydroxybutyrate* ((2R,3S)-**3**). $[\alpha]_D^{22}$ ($c = 0.34$) = + 5.83°; e.e. ~ 100%. NMR (360 MHz): δ 5.85–5.75 (m, 1 vinyl proton), 5.15–5.0 (m, $=CH_2$), 4.18 (q, $-O-CH_2-$), 4.06–3.98 (after addition of D_2O d × q, J(2,3) = 4.78 Hz, H–C(3)), 2.55–2.35 (m, H–C(2) and 2H–(C')), 1.28 (t, CH_3-CH_2-), 1.22 (d, 3H–C(4)) ppm.

Reduction of ethyl 2-*benzylacetoacetate* (**15**) *to ethyl* (2RS,3S)-2-*benzyl*-3-*hydroxybutyrate* ((2S,3S)-**4**). 10 g of **15** was reduced with baker's yeast in the same manner as described above. After work up the crude product mixture (7.8 g) was chromatographed on silica gel with hexane ether (1:1). After elution of 4.5 g (45%) of educt, 2.2 g (22%) of a 65:35 mixture of (2*S*,3*S*)-**4** and (2*R*,3*S*)-**4** was isolated. The main product corresponded to (2*S*,3*S*)-**4**. Preparative GLC was used to separate the two diastereomers. (2*S*,3*S*)-**4**: $[\alpha]_D^{22}$ ($CHCl_3$, $c = 0.75$) = − 35.85°; e.e. ~ 100%, no isomer detectable in GLC, none either in the NMR with lanthanide-shift reagents (Eu(hfc)$_3$). The NMR was identical to the one already described for the alkylation product. (2*R*,3*S*)-**4**: $[\alpha]_D^{22}$ ($c = 0.93$) = + 35.46° GLC shows 7% of (2*S*,3*S*)-**4** as an impurity. This corrects $[\alpha]_D^{22}$ to +40.8°. NMR (360 MHz): δ 7.3–7.15 (m, 5 aromatic H), 4.1–4.0 (m,

–O–CH_2–, and H–C(3)), 3.01–2.95 (m, –CH_2–Ar), 2.76–2.72 (m, J(2,3) = 4.4 Hz, H–C(2)), 2.48 (broad s, OH), 1.27 (d, 3H–C(4)), 1.09 (t, CH_3–CH_2–) ppm.

Ethyl (2R,3S) - 2 - *allyl* - 2 - *methyl* - 3 - *hydroxybutyrate* ((2R,3S)-**11**. At −50° 3.44 g (20 mmole) of the above described mixture of (2*RS*,3*S*)-**3** in 20 ml THF was added to 40 mmole of lithium cyclohexylisopropylamide in 50 ml THF. The temp was allowed to reach −20° (*ca* 15 min). At this point 3 g (22 mmole) of MeI dissolved in 5 ml HMPTA was added quickly and the temp rose to +10°. Stirring was continued for 15 min. The mixture was poured on sat NH_4Claq and extracted with ether. The crude yield amounted to 3.5 g: GLC (XF 1155, 3 m) showed an educt-product ratio of *ca* 1:4, the products having been formed with a stereoselectivity of *ca* 95:5. Flash chromatography on silica gel with hexane–ether (6:4) furnished a main fraction of 2.1 g (56%) of the title compound (isomer ratio slightly enriched to 98:2) and a second fraction of 1.3 g contaminated with the educt. The main fraction was distilled (Kugelrohr): B.p. 55–60° at 0.15 mm Hg. $[\alpha]_D^{22}$ (*c* = 0.65) = +14.6°. NMR (+D_2O, 100 MHz): δ 6.0–5.6 (1 vinyl proton), 5.2–5.0 (=CH_2), 4.18 (q, O–CH_2–), 3.92 (q, H–C(3)), 2.7–2.1 (ABX-pattern of –CH_2–CH=), 1.27 (t, O–CH_2–CH_3) 1.16 (d, 3H–C(4)), 1.15 (s, CH_3–C(2)) ppm. (Found: C, 64.2; H, 9.87. Calc for $C_{10}H_{18}O_3$ (186.25): C, 64.49; H, 9.74%.)

Ethyl (2S,3S) - 2 - *allyl* - 2 - *methyl* - 3 - *hydroxybutyrate* ((2S,3S)-**11**). To the soln of 60 mmole of lithium cyclohexylisopropylamide in 50 ml THF, 4.4 g (30 mmole) of the above described mixture of (2*RS*,3*S*)-**2** in 20 ml THF was added at −50°. In the course of the addition (*ca* 15 min) the temp rose to −20°. Then 4.0 g (33 mmole) allyl bromide solved in 10 ml HMPTA was added quickly, the temp rising to +10–15°. The mixture was worked up with $2NH_2SO_4$ and pentane furnishing a crude yield of 4.8 g of a *ca* 1:3 mixture of educt and product. The latter was formed with a stereoselectivity of about 94:6. Flash-chromatography on silica gel with hexane–ether (6:4) furnished the title compound as the main fraction 3.2 g (57%) with a ratio of *ca* 95% (2*S*,3*S*)-**11** and 5% (2*R*,3*S*)-**11**. B.p. (Kugelrohr): 55–60° at 0.15 mm Hg. $[\alpha]_D^{22}$ (*c* = 0.63) = +7.6°. NMR (100 MHz): δ 5.95–5.55 (1 vinyl proton), 5.2–4.95 (=CH_2), 4.2 (q, –O–CH_2–), 3.98 (d × q, D_2O→q, H–C(3)), 2.71 (d, OH), 2.6–2.15 (ABX-pattern of –CH_2–CH=), 1.28 (t, –O–CH_2CH_3), 1.16 (d, 3H–C(4)), 1.13 (s, CH_3–C(2)) ppm. (Found: C, 63.31; H, 9.89. Calc for $C_{10}H_{18}O_3$ (186.25): C, 64.49; H, 9.74%.)

Ethyl (R)-2-*acyl*-2-*methyl*-4-*pentenoate* ((R)-**16**). To 230 mg (1.24 mmole) (2*R*,3*S*)-**11** dissolved in 2 ml ether the soln of 370 mg of sodium bichromate and 345 mg of conc H_2SO_4 in 1 ml H_2O was slowly added at maximum 3°. After 10 min of additional stirring the mixture was worked up and 220 mg of a slightly brownish oil was isolated. Chromatography on silica gel with hexane–ether (1:1) yielded 182 mg (82%) of the ketone beside 35 mg of educt. B.p. (Kugelrohr): 55–60°, 0.02 mm Hg. $[\alpha]_D^{22}$ (*c* = 1.17) = +28.5°, e.e. ~96%. IR (film): 1740, 1717 cm^{-1}. NMR (100 MHz): δ 5.9–5.5 (m, 1 vinyl proton), 5.22–5.0 (m, =CH_2), 4.2 (q, O–CH_2–), 2.8–2.35 (M, ABX-pattern of 2H–C(3)), 2.15 (s, CH_3–CO–), 1.32 (s, CH_3–C(2)), 1.26 (t, CH_3–CH_2–) ppm. (Found: C, 65.28; H, 8.86. Calc for $C_{10}H_{16}O_3$ (184.24): C, 65.19; H, 8.75%.)

Ethyl (S)-2-*acyl*-2-*methyl*-4-*pentenoate* ((S)-**16**). Analogous oxidation of (2*S*,3*S*)-**11** yielded in 81% yield (*S*)-**16**. $[\alpha]_D^{22}$ (*c* = 0.9) = −27.05° (e.e. ~91%).

Baker's yeast reduction of rac ethyl 2-*acyl*-2-*methyl*-4-*pentenoate* (*rac* **16**). 5 g (27 mmole) racemic **16**, 50 g baker's yeast, 75 g saccharose in 500 ml tapwater was stirred for 42 hr. Work up yielded 3.5 g of a yellowish oil. Chromatography on silica gel with hexane–ether (1:1) yielded after distillation (Kugelrohr) at 55° (0.05 mm Hg) 1.9 g (38%) (*R*)-**16**, with $[\alpha]_D^{22}$ (*c* = 0.96) = +8.1° (e.e. ~27.5%) and 1.0 g (20%) of (2*S*,3*S*)-**11**, $[\alpha]_D^{22}$ ($CHCl_3$, *c* = 1.0) = +7.84°.

Oxidation of this sample of (2*S*,3*S*)-**11** in analogy to the above described experiments furnished in 80% yield optically pure (*S*)-**16** with $[\alpha]_D^{22}$ (*c* = 0.83) = −29.6°. Optishift with Eu(hfc)$_3$: rac **16** gave a good separation of the acetyl group, which could not be observed in this sample.

Ethyl (2S) - 5 - *chloro* - 2((S) - 1 - *hydroxyethyl*) - 2 - *methyl* - 4 - *hexenoate* ((S,S) - **17**). 8.8 g (60 mmole) of (2*RS*,3*S*)-**2** was added to 0.12 mole of lithium cyclohexylisopropylamide in 100 ml THF and 75 ml ether at −60°. The temp rose to −30°. At this temp 14 g (65 mmole) of *E*,*Z*-1-iodo-3-chloro-2-butene dissolved in 30 ml HMPTA was added quickly at which the temp rose to +10°, After stirring for 15 min at 10° the mixture was worked up with $2NH_2SO_4$ and ether. The crude product (15 g) was distilled at 100° and 0.05 mm Hg to give 9.8 g of distillate, which was chromatographed on silica gel with hexane–ether (1:1). After 1.7 g of nonpolar material 7.5 g (53%) of *E*,*Z*-(*S*,*S*)-**17** was eluted. B.P. 80° at 0.03 mm Hg (Kugelrohr). $[\alpha]_D^{22}$ (*c* = 1.35) = 0.81°. NMR (360 MHz): δ 5.37–5.32 and 5.4–5.35 (each a t × q, ~1:4, H–C(4)), 4.23–4.16 (q, –O–CH_2–), 3.93–3.86 and 3.84–3.78 (after addition of D_2O each a q, ~4:1, H–C(1')), 2.73 and 2.65 (2d, OH), 2.6–2.39 (AB-pattern of 2H–C(3)), 2.1 and 2.06 (sharp multiplets, 3H–C(6)), 1.29 (t, CH_3–CH_2–O), 1.16 (d, 3H–C(2')), 1.14 (s, CH_3–C(2)) ppm.

Ethyl (S)-2-*acetyl*-5-*chloro*-2-*methyl*-4-*hexenoate* ((S)-**18**). 4 g (17 mmole) of (*S*,*S*)-**17** was oxidized as described for (*S*) and (*R*)-**16** to give after chromatography (silica gel, hexane–ether (1:1)) 3.5 g (87.5%) (*S*)-**18**. $[\alpha]_D^{22}$ (*c* = 1.2) = −27–86°. Both GLC and NMR showed the *E*/*Z*-isomers. NMR (360 MHz): only the main isomer: δ 5.33 (q × t, H–C(4)), 4.2 (q, –O–CH_2–), 2.72 (d × q, 2H–C(3)), 2.16 (s, 3H–C(2')), 2.09 (sharp m, 3H–C(6)), 1.35 (s, CH_3–C(2)), 1.26 (t, CH_3–CH_2–) ppm.

Ethyl (S)-2-*acetyl*-2-*methyl*-5-*oxohexanoate* ((S)-**19**). 3.2 g (14 mmole) (*S*)-**18** was added to the soln of 8.3 g (20 mmole) of mercury trifluoroacetate in 50 ml nitromethane. The mixture was stirred for 45 hr at ambient temp and then poured into 200 ml 10% HCl. It was extracted three times with ether. The crude product (3.8 g) was distilled at 100–110° and 0.05 mm Hg (Kugelrohr) to give 2.6 g of material. This was chromatographed on silica gel with hexane–ether (1:1) giving the following fractions: 0.3 g educt and unidentified materials, 350 mg of a 4:1 mixture of (*S*)-**21** and probably **22** and 1.8 g (60%) of (*S*)-**19**. B.p. (Kugelrohr) 80–85° at 0.05 mm Hg. $[\alpha]_D^{22}$ (*c* = 1.3) = −8.32°. NMR (360 MHz): δ 4.23–4.16 (m, –O–CH_2–), 2.45–2.39 (m, 2H–C(4)), 2.16 (s, CH_3–), 2.14 (s, CH_3–), 2.15–2.10 (m, 2H–C(3)), 1.34 (s, CH_3–C(2)), 1.27 (t, CH_3–CH_2—) ppm.

Optishift with this material showed an enantiomeric ratio of *ca* 93:7 by means of splitting up the singlets at 2.16 and 2.14 ppm. (Found: C, 61.73; H, 8.35. Calc for $C_{11}H_{18}O_4$ (214.26): C, 61.66; H, 8.74%.)

Ethyl (S) - 1,2 - *dimethyl* - 4 - *oxo* - 2 - *cyclohexene* - 1 - *carboxylate* ((S) - **20**). 107 mg (0.5 mmole) (*S*)-**19**, 30 mg pyrrolidine and 28 mg AcOH was stirred in 5 ml ether for 20 hr at ambient temp. Work up with water and ether furnished in virtually quantitative yield 95 mg (*S*)-**20**. The isomer (*S*)-**21** could not be detected in GLC or NMR. B.p. (Kugelrohr: 90–95° at 0.05 mm Hg. $[\alpha]_D^{22}$ (*c* = 1.15) = −106.5°; $[\alpha]_D^{22}$ (benzene, *c* = 1.32) = −116.2°. IR (film): 1728, 1677 cm^{-1}. NMR (360 MHz): δ 5.92 (q, H–C(3)), 4.2 (q, –O–CH_2–), 2.53–2.38 (m, 3H), 1.96 (d, J ~ 1.6 Hz, CH_3–C(2)), 2.0–1.9 (m, 1H), 1.43 (s, CH_3–C(1)), 1.28 (t, CH_3–CH_2–) ppm.

Optishift experiments with Eu(hfc)$_3$ confirmed the measurements with (*S*)-**19**, as the t at 1.28 ppm separated into two triplets in a ratio of about 94:6. (Found: C, 67.08; H, 8.40. Calc for $C_{11}H_{16}O_3$ (196.25): C, 67.32; H, 8.22%.)

Ethyl (S) - 1,4 - *dimethyl* - 2 - *oxo* - 3 - *cyclohexene* - 1 - *carboxylate* ((S) - **21**). 200 mg (0.93 mmole) (*S*)-**19** and 20 mg TosOH in 10 ml toluene were heated to reflux for 25 min. Then the mixture was washed with $NaHCO_3$, dried

and the toluene evaporated. The crude product (222 mg) was a *ca* 4:1 mixture of (*S*)-**21** and (*S*)-**20**, which were separated by chromatography on silica gel with hexane–ether (3:7). First 134 mg (*S*)-**21** was eluted, then 35 mg of 1:2 mixture of (*S*)-**21** and (*S*)-**20** and finally 31 mg pure (*S*)-**20**. The pure fractions were distilled in Kugelrohr yielding 110 mg (48.5%) ((*S*)-**21** and 26 mg (11%) (*S*)-**20**. (*S*)-**21**: $[\alpha]_D^{22}$ ($c = 1.5$) = + 55.3°; $[\alpha]_D^{22}$ (benzene, $c = 1.0$) = + 44.1°. IR ($CHCl_3$): 1725, 1655 cm^{-1}. NMR (360 MHz): δ 5.9 (m, H–C(3)), 4.15 (q, O–CH_2–), 2.51–2.38 (m, 2H), 2.3–2.2 (m, 1H), 1.95 (sharp m, CH_3–C(4)), 1.91–1.83 (m, 1H), 1.47 (s, CH_3–C(1)), 1.23 (t, CH_3–CH_2–) ppm. Double resonance experiments revealed a small coupling between CH_3–C(4) and CH_2(5) of *ca* 1 Hz and also between H–C(3) and CH_2(5). (Found: C, 67.42; H, 8.25. Calc for $C_{11}H_{16}O_3$ (196.25): C, 67.32; H, 8.22%.)

Ethyl (2S)-2((S)-1-*hydroxyethyl*)-2-*methyl*-4-*hexenoate* ((S,S)-**23**). 29.3 g (0.2 mole) (2*RS*,3*S*)-**2** was alkylated in analogy to the preparation of (2*S*,3*S*)-**11** with crotyl bromide. The crude material (40 g) was distilled and the fraction boiling at 80–85° and 0.1 mm Hg (27 g) was purified on silica gel with hexane–ether (1:1) to give 25 g of an oil, which after distillation in Kugelrohr at 70–75° and 0.05 mm Hg furnished 24 g (60%) of (*S,S*)-**23**. It was estimated from the GLC and NMR spectra that this material consisted of *ca* 80% *E*-(*S,S*)-**23** and *ca* 20% *Z*-(*S,S*)-**23**. The stereoselecitivity was 95:5. $[\alpha]_D^{22}$ ($c = 1.1$) = + 5.9°. NMR (400 MHz) of the main isomer: 5.53–5.28 (m, H–C(4), H–C(5), J(4,5) = 15 Hz), 4.21–4.14 (m, –O–CH_2–), 3.9–3.82 (after addition of D_2O q, H–(C–1′)), 2.73 (broad d, OH), 2.38–2.19 (AB-pattern of 2H–C(3)), 1.66–1.64 (m, 3H–C(6)), 1.28 (t, CH_3–CH_2), 1.14 (d, CH_3–C–), 1.1 (s, CH_3–C(2)). (Found: C, 65.68; H, 9.94. Calc for $C_{11}H_{20}O_3$ (198.2): C, 65.97; H, 9.94%.)

(2S,3R) - 3 - *Hydroxymethyl* - 3 - *methyl* - 5 - *hepten*-2 - *ol* ((2S,3R)-**24**). 2.8 g (73 mmole) $LiAlH_4$ was suspended in 50 ml ether and 15 g (75 mmole) (*S,S*)-**23** in 50 ml ether was added dropwise between 20–30°. After reduction was completed the mixture was worked up with water and ether furnishing 9.9 g (83%) (2*S*,**R*)-**24** with a b.p. of 85–90° at 0.05 mm Hg. $[\alpha]_D^{22}$ ($c = 1.6$) = − 1.69°. NMR (400 MHz) of the main isomer, *E*-(2*S*,3*R*)-**24**: δ 5.53–5.41 (m, H–C(5), H–C(6)), 3.78 (q after D_2O addition, H–C(2)), 3.66 and 3.48 (AB-q of 2H–C(1′)), 3.0–2.8 (two broad signals 2 × OH), 2.11–2.07 (m, 2H–C(4)), 1.7–1.66 (m, 3H–C(7)), 1.19 (d, 3H–C(1)), 0.77 (s, CH_3–C(3)) ppm. (Found: C, 68.05; H, 11.52. Calc for $C_9H_{18}O_2$ (158.24): C, 68.31; H, 11.47%.)

(2S,3R) - 3((t - *Butyldimethylsilyloxy*)*methyl*) - 3 - *methyl*-5 - *hepten* - 2 - *ol* ((2S,3R)-**25**). A soln of 6.7 g (45 mmole) of t-butyldimethylchlorosilane in 50 ml DMF was added dropwise to a soln of 7.1 g (44.8 mmole) (2*S*,3*R*)-**24** and 6.1 g (90 mmole) imidazole in 150 ml DMF at ambient temp.[43] After 1 hr the mixture was poured into water and extracted with ether. Distillation (Kugelrohr) at 75° and 0.05 mm Hg gave 10.8 g (87.1%) (2*S*,3*R*)-**25** as a colourless oil. $[\alpha]_D^{22}$ ($c = 2.0$) = + 1.18°. NMR (400 MHz) of the main E-isomer: δ 5.5–5.38 (m, 2H), 3.69 (q after D_2O addition, H–C(2)), 3.59 and 3.48 (AB-pattern of 2H–C(1′)), 2.13–2.0 (m, 2H–C(4)), 1.58–1.55 (m, 3H–C(7)), 1.15 (d, 3H–C(1)), 0.9 (s, 9H), 0.75 (s, CH_3–C(3)), 0.08 (s, 6H) ppm. (Found: C, 65.94; H, 11.93. Calc for $C_{15}H_{32}O_2Si$ (272.51): C, 66.11; H, 11.84%.)

(R) - 3 - ((t - *Butyldimethylsilyloxy*)*methyl*) - 3 - *methyl*-5 - *hepten* - 2 - *one* ((R)-**26**). 10.2 g (37 mmole) (2*S*,3*R*)-**25** were oxidized in analogy to the procedure described.[44] The reaction yielded after distillation (Kugelrohr) 65°, 0.05 mm Hg, 8.0 g (80%) (*R*)-**26**. $[\alpha]_D^{22}$ ($c = 2.2$) = − 0.77°. NMR (400 MHz) of the main isomer: δ 5.5–5.42 (m, 1H), 5.32–5.23 (m, 1H), 3.64 and 3.52 (AB-pattern of 2H-(C′)), 2.33–2.36 and 2.13–2.07 (m, 2H–C(4)), 2.13 (s, 3H–C(1)), 1.66–1.63 (m, 3H–C(7)), 1.07 (s, CH_3–C(3)), 0.87 (s, 9H), 0.03 (s, 6H ppm. Upon treatment with $Eu(hfc)_3$ the signal at 2.13 ppm splitted up in two s at a ratio of *ca* 94:6. (Found: C, 66.46; H, 11.28. Calc for $C_{15}H_{30}O_2Si$ (270.49): C, 66.61; H, 11.18%.)

(R) - 3 - (*Hydroxymethyl*) - 3 - *methyl* - 5 - *hepten* - 2 - *one* ((R)-**27**). 7.45 g (27.5 mmole) (*R*)-**26** and 14.17 g (45 mmole) dry tetrabutylammonium fluoride in 100 ml THF were stirred for 2 hr at ambient temp. After work up with water and ether the oil was distilled (Kugelrohr 85° and 10 mm Hg) to give 4.0 g (93%) (*R*)-**27**.$[\alpha]_D^{22}$ ($c = 2.9$) = + 16.6°. NMR (400 MHz): δ 5.57–5.48 (m, 1H), 5.38–5.29 (m, 1H), 3.69 and 3.46 (AB-q of 2H–C(1′)), 2.33 (broad, s, OH), 2.3–2.18 (m, 2H–C(4)), 2.15 (s, 3H–C(1)), 1.68–1.64 (sharp m, 3H–C(7)), 1.14 (s, CH_3–C(3)) ppm. (Found: C, 68.85; H, 10.46. Calc for $C_9H_{16}O_2$ (156.23): C, 69.19, H, 10.32%.)

(R) - 2 - *Acetyl* - 2 - *methyl* - 4 - *hexenyl* p - *toluenesulfonate* ((R)-**28**). 3.5 g (22 mmole) (*R*)-**27** and 4.5 g (24 mmole) tosyl chloride in 30 ml pyridine were standing at 5° for 48 hr. After work up and flash-chromatography on silica gel (hexane–ether 1:1) 6.1 g (89%) (*R*)-**28** was isolated as a colourless oil. $[\alpha]_D^{22}$ ($c = 1.67$) = + 2.04°. NMR (400 MHz): δ 7.78 and 7.36 (m, 4H), 5.45–5.36 (m, 1H), 5.13–5.04 (m, 1H), 4.05 (AB-q, J(gem) ~ 10 Hz, 2H–C(1)), 2.45 (s, CH_3-arom.), 2.28–2.13 (AB-m, 2H–C(3)), 2.09 (s, CH_3–CO–), 1.58–1.55 (d × m, 3H–C(6)), 1.14 (s, CH_3–C(2)) ppm. (Found: C, 62.04; H, 7.18; S, 9.97. Calc for $C_{16}H_{22}O_4S$ (310.41): C, 61.91; H, 7.14; S, 10.33%.)

(R) - 3 - (2 - *Butenyl*) - 3 - *methyl*- -2 - *methyleneoxetane* ((R)-**30**) *and* (S) - 2 - (2 - *butenyl*) - 2 - *methylcyclobutanone* ((S) - **29**). 2.4 g (7.7 mmole) (*R*)-**28** was stirred in the soln of 8 ml 1 Mt-BuOK in t-BuOH and 16 ml THF for 10 min at ambient temp. After work up the crude oil (0.95 g) was chromatographed on silica gel with pentane–ether (9:1). The first fraction gave after distillation (Kugelrohr ~ 80° at 150 mm Hg) 460 mg (43%) (*R*)-**30**. $[\alpha]_D^{22}$ ($c = 1.5$) = + 76.3°. IR (film): 1690, 966 cm^{-1}. NMR (400 MHz) of the main E-isomer: δ 5.58–5.42 (m, 2H), 4.43 and 4.39 (two d, J ~ 5.5 Hz, =CH_2), 4.02 and 3.68 (two d, J(gem) ~ 4 Hz, 2H–C(4)), 2.36–2.2 (AB-m, J(gem) ~ 14 Hz, 2H–C(1′)), 1.71–1.67 (d × m, 3H–C(4′)), 1.31 (s, CH_3–C(3)). (Found: C, 78.02; H, 10.45. Calc for $C_9H_{14}O$ (138.21): C, 78.21; H, 10.21%.) The second fraction yielded after distillation (Kugelrohr, ~ 80° at 150 mm Hg) 360 mg (34%) (*S*)-**29**. $[\alpha]_D^{22}$ ($c = 1.5$) = − 103.7° $\Delta\epsilon$ (EPA): (306) = − 1.56. IR (film): 1780, 968 cm^{-1}. NMR (400 MHz) of the main E-isomer: δ 5.56–5.34 (m, 2H), 3.03–2.88 (m, 2H–C(4)), 2.27–2.1 (AB-m of 2H–C(1′)), 2.0–1.9 (m, H–C(3)), 1.74–1.65 (m, H′–C(3)), superimposed 1.7–1.65 (d × m, 3H–C(4′)), 1.16 (s, CH_3–C(2)). (Found: C, 78.19; H, 10.27. Calc for $C_9H_{14}O$ (138.21): C, 78.21; H, 10.21%.)

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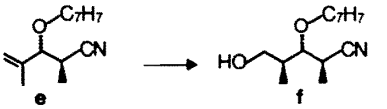

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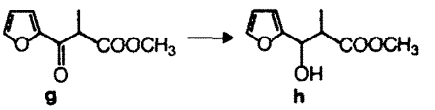

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