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Enantio- and Diastereoselective Synthesis of the AB Ring System of Aklavinone by Coupling a Chemoenzymatic Procedure with Organometal Chemistry[1]

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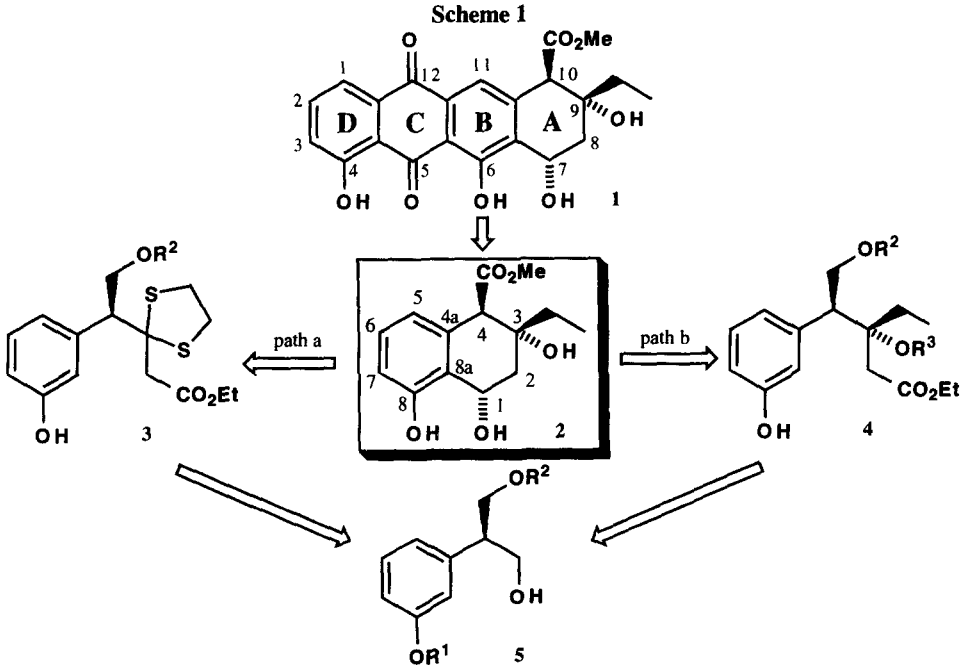
Abstract: Two different approaches were investigated in order to prepare the title compound **2**; best results were obtained when the tandem reduction/intramolecular hydroxyalkylation of the appropriate 5-alkoxy-(3-hydroxyphenyl)pentanoate was performed on an ester of chemoenzymatic origin, already bearing the two chiral centers present in **2** with the correct relative and absolute stereochemistry. Copyright © 1996 Elsevier Science Ltd

Scheme 1



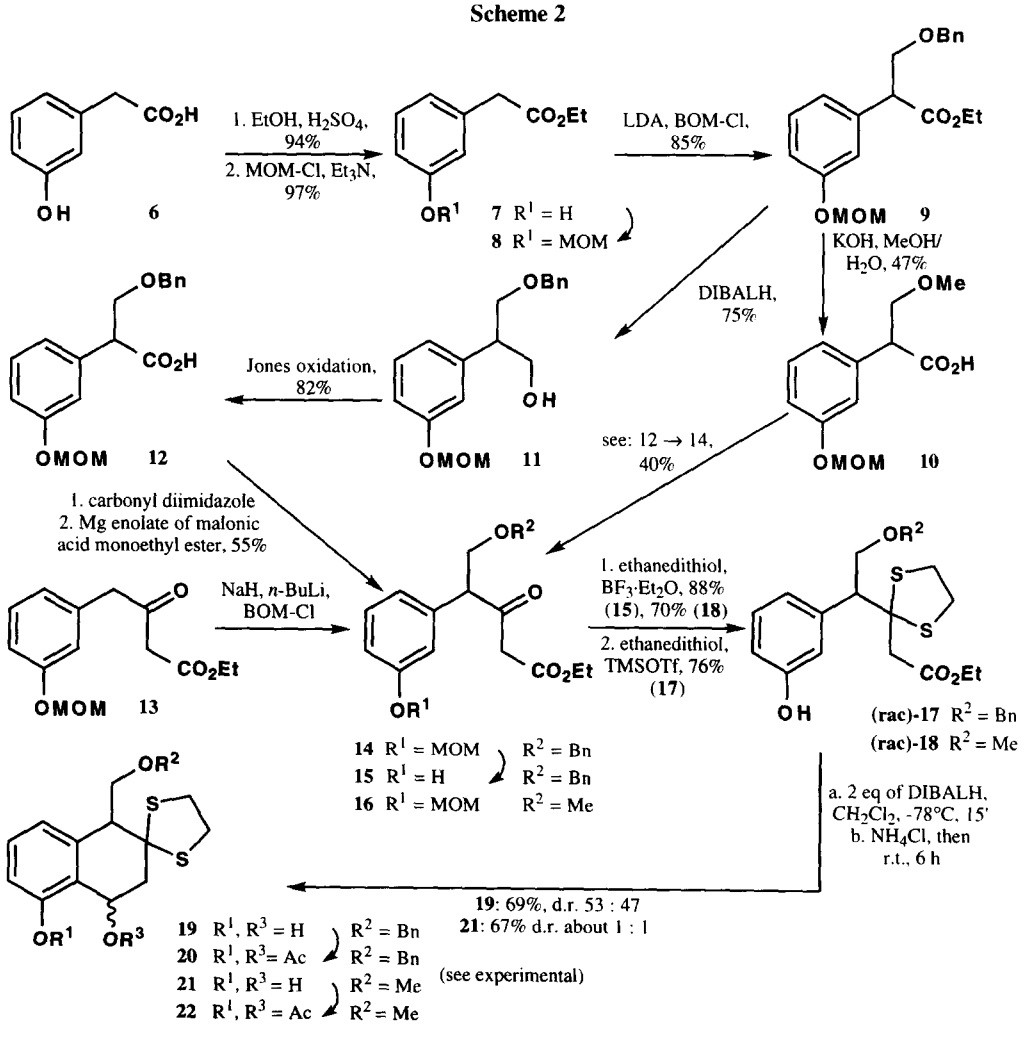
In the last years many efforts in the field of organic synthesis have been devoted to the preparation of natural compounds of known biological activity. Within this area we have been interested in the chemistry of anthracyclinones, particularly of the 11-deoxyanthracyclinone antibiotics, the most interesting being Aklavinone **1**, a compound characterized by a significant anticancer activity.[2] The absence of hydroxy groups

in positions 1 and 11 reduces the symmetry of the molecule, thus requiring an accurate choice of reaction conditions in order to ensure a regioselective assemblage of the intermediates.

In the past some enantioselective synthetic approaches to **1** have been published.[3] In this paper we describe a new enantio- and diastereoselective synthesis of the AB moiety **2**, in which the crucial step is the regioselective formation of ring A starting from a chiral 5-alkoxy-(3-hydroxyphenyl)pentanoate, obtained through a chemoenzymatic procedure. The possibility of controlling the regioselectivity during the ring closure was previously investigated by us on simpler substrates[4] and so we hoped to be able to extend our protocol also on more functionalized optically active systems.

For the synthesis of **2** we envisaged two possible procedures as described in Scheme 1, both starting from a similar chiral synthon of general formula **5**. The two synthetic approaches involved the preparation of pentanoates **3** and **4** in order to submit them to the intramolecular and regioselective cyclization reaction, which have been carefully monitored by us on several model compounds.[4] However, the difference lies in the fact that path *a* requires the introduction of the second chiral centre on the preformed 1,8-dihydroxytetralin system, presumably *via* the diastereoselective addition of an organometallic compound to a cyclic ketone.

Scheme 2



while in path *b* the second chiral centre has to be formed by addition of an organometallic to an acyclic ketone, thus requiring a different approach for diastereoselection control.

So, we first investigated path *a* which, in principle, seemed to be simpler. First of all we studied a racemic synthesis of an intermediate like **3**, whose preparation is summarized in Scheme 2, hoping to repeat a similar procedure for the optically active compound. Initially, we tried to use β-ketoester **13**, previously prepared by us,[4] as starting material, having in mind to alkylate its dianion with benzyl chloromethyl ether.[5,6] However, this reaction proved to be troublesome; although the reaction seemed to be rather clean by t.l.c. analysis, we always obtained very low yield of **14** after chromatography: probably, the presence of some by-products of acidic nature, derived from decomposition of BOM-Cl, was responsible of an extended decomposition of **14** during purification.[7]

That is why we choose to follow a longer reaction sequence, starting from 3-hydroxyphenylacetic acid **6**, easily transformed into the protected ester **8**; the lithium enolate of the latter compound was treated with BOM-Cl to give **9** in good yield. At this point we thought to hydrolize the ester function but, to our surprise, standard conditions used for this purpose did not give acid **12**. Actually, we isolated only moderate quantities of the β-methoxyacid **10**.[8]

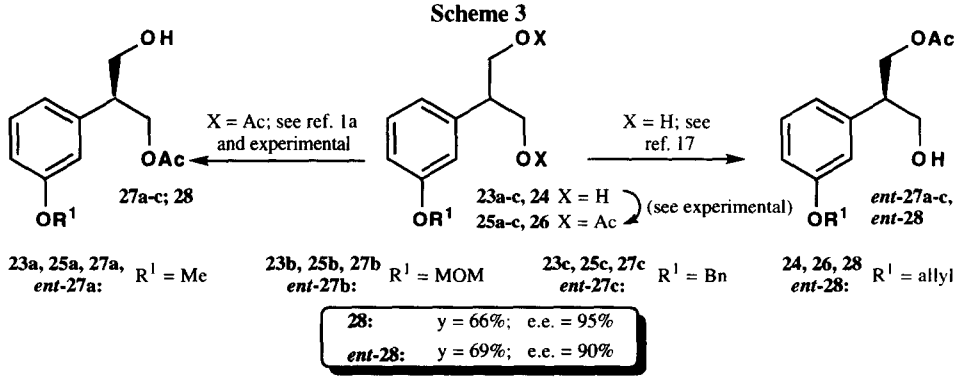
Due to the instability of **9** under basic conditions we had to prepare acid **12** by reduction of the corresponding ester to the alcohol **11**, followed by its oxidation with Jones reagent.[9] The homologation to give the β-ketoester **14**[10] has been realized by treating *in situ* the imidazolide derived from **12** with the magnesium enolate of malonic acid monoethyl ester.[11]

However, an intermediate suitable for our previously described cyclization protocol[4] must have a free phenolic group and had to be protected at the carbonyl function to avoid undesired aromatization processes as predictable side reactions. As we experienced before, the dithiolane is undoubtedly the protecting group of choice for the carbonyl group. While the methylether **16** gave dithiolane **18** without problems under classical conditions (ethanedithiol, $BF_3{\cdot}Et_2O$), the transformation of **14** into **17** was troublesome. These conditions gave indeed also benzylether cleavage,[12] in addition to nearly instantaneous deprotection of phenol group.[13] In order to avoid this side reaction, probably provoked by the soft nucleophilicity of ethanedithiol, we thus employed an original methodology,[14] that is: a) a very fast reaction with ethanedithiol/ $BF_3{\cdot}Et_2O$ to eliminate MOM protecting group giving intermediate **15** and b) its reaction with ethanedithiol pre-silylated by *in situ* treatment with trimethylsilyltriflate (without added base). By this methodology thioketalization took place in good yields without affecting the benzyl ether.

As the last step we applied our cyclization protocol[4] either to **17** or to **18** and in both cases we obtained regioselectively the corresponding 1,8-dihydroxytetralins **19** and **21** with good chemical yield,[15] albeit with very low diastereoselection. This fact was not completely unexpected, because the incipient chiral centre is too far away from the pre-existing one.

After achieving the synthesis of **19** in racemic form we tried to apply an analogous protocol to the

Scheme 3



preparation of the optically active 1,8-dihydroxytetralin system.

For this purpose we needed a suitable chiral synthon like **5** and then we had to transform it into the target molecule, following a non-racemizing sequence. Compound **5** belongs to the family of the 1,3-propanediols substituted in position 2, whose asymmetrization employing hydrolytic enzymes was extensively studied in the past in our research group both using monohydrolysis reactions of prochiral diacetates[16] or monoacylation reactions of the diols in organic solvents.[17]

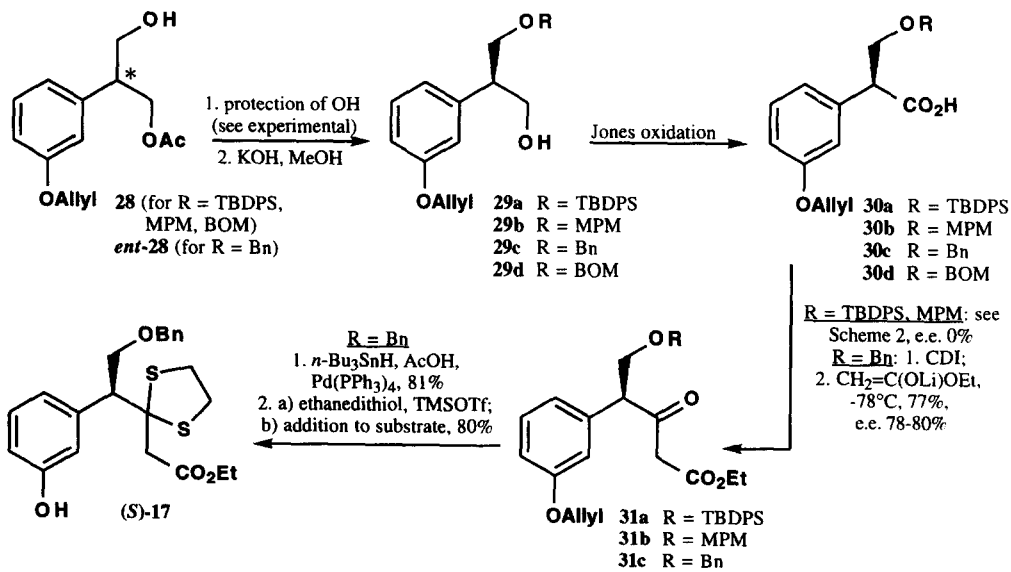
We thus studied the factors affecting the enantioselectivity and the chemical yields in the preparation of both enantiomers of monoacetates of general formula **27a-c, 28** and ***ent*-27a-c, *ent*-28** (differing only in the protecting group of the phenolic function) by enzyme-catalyzed asymmetrization of the corresponding diacetates (Lipase from porcine pancreas) and of the corresponding diols (Lipase from porcine pancreas supported on celite). The results of this investigation, as well as the determination of absolute configurations of the monoacetates, have been previously reported.[1a,17] For our synthetic purposes we choose allyl as best protecting group for the phenolic function for a series of reasons: a) both enantiomers of the two monoacetates can be obtained in good chemical yield and with high enantiomeric excess:[18] **28** from diacetate **26**, ***ent*-28** from diol **24**,[19] as summarized in Scheme 3; b) this group seemed to be consistent with the planned synthetic elaboration; c) allyl group should be easily removed just before the final cyclization reaction without affecting other functional groups in the molecule.

The elaboration of **28** or its enantiomer followed first path *a*. Our experience in preparing racemic **19** and **21**, suggested to protect the primary alcoholic function with a more sterically demanding group than benzyl, in order to possibly affect the diastereomeric ratio in the intramolecular cyclization process.[20] This is why we prepared in high yield and without racemization TBDPS O-protected alcohol **29a**,[21] starting from monoacetate **28**, hoping to take advantage from the bulkiness of this silylated group (Scheme 4).

The transformation of **29a** into **31a** followed the protocol described in Scheme 2 (**11** → **14**). The protection of the ketone function to give the corresponding dithiolane was in this case troublesome: also trying different reaction conditions, we never succeeded in this transformation.[22] Since we knew that also the dioxolane protection should be suitable for the final cyclization,[4] we tried also transformation into this moiety, but without success.[23]

So, we turned back to the use of benzyl as protecting group and prepared **29c** from **28**. Direct protection

Scheme 4



of monoacetate **28** under various conditions was however either racemizing[24a,b] or proceeded in unsatisfactory yields.[24c] On the other hand, the direct introduction of the *p*-methoxybenzyl (MPM) group, using *p*-methoxybenzyl trichloroacetimidate in the presence of camphorsulphonic acid[24c] was successful (78% yield, no racemization observed), but, after the usual transformation of **29b** into **31b**, we were not able to introduce the dithiolane protection.[25] The same happened when we tried to protect the ketone as dioxolane.

In order to circumvent the racemization problem we optimized a longer procedure for obtaining **29c**, that is a protecting group manipulation which introduced the benzyl on the alkoxide obtained after acetate saponification of ***ent*-28** and -CH_2OH protection as tetrahydropyranyl ether. In this case, in order to have the correct absolute stereochemistry at the chiral centre, we had to utilize ***ent*-28**, prepared from the enzymatic acetylation of **24**.[26]

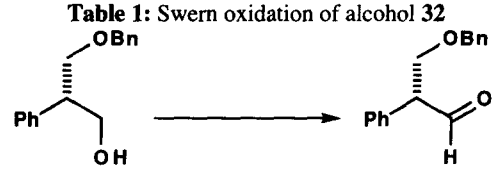
The homologation step required to obtain **31c** was first attempted by the same procedure employed for racemic **12**. However, this methodology turned out to be completely racemizing.[27]

After many attempts[29] the most satisfactory results for the preparation of **31c** were obtained by reaction of the imidazolide of **30c** with the lithium enolate of ethyl acetate at -78°C. Finally, **31c** was protected as dithiolane and the phenolic function deblocked to give optically active (***S*)-17**, which was submitted to the cyclization protocol already described in Scheme 2 for the racemate. Also in this case we demonstrated that the procedure was not free from racemization.[30] Actually, e.e. dropped from 90% to 78-80%.

The two carbon elongation of the unprotected arm of **29c** should in principle derive also from a suitable organometal addition to the aldehyde obtained from controlled oxidation of the alcoholic function, followed by the oxidation of the secondary alcohol to the corresponding ketone.

Having in mind this procedure we first studied on model compound **32**[31] the preparation of the aldehyde **33**, focusing our attention on the possible but undesired racemization of this intermediate. Actually, compounds very similar to **33**, as for example 2-phenylbutyraldehyde are known as very easily racemizable substrates[32] and so our project was really intriguing, although probably difficult to realize. Also in the past we found that traditional Swern oxidation is not always the methodology of choice to avoid racemization during the transformation of an alcohol into an aldehyde.[33] In this case, use of a less basic and more hindered amine (Hünig's base) instead of the usual triethylamine,[34] followed by a slightly acidic work-up, allowed to obtain the oxidation product without racemization. In our case, as reported in Table 1, we noticed that usual Swern oxidation gave complete racemization,[35] together with only a moderate yield.[36] Moreover, also use of Et*i*-Pr_2N (entry 2), although less racemizing, was not completely satisfactory; otherwise, a little better result was obtained if the oxidation was performed in toluene instead of the usual methylene chloride (entry 3), but

Table 1: Swern oxidation of alcohol **32**



32 33

Entry	*Solvent*	*Base*	*$(COCl)_2$/DMSO/Base (mmols/mmols of 32)*	*Temperature (°C)*	*Time (h)*	*Yield[a] (%)*	*Racemization (%)*
1	CH_2Cl_2	Et_3N	2.5 : 4 : 7	- 74° → - 40°	2	51	complete
2	CH_2Cl_2	Et*i*-Pr_2N	2.5 : 4 : 7	- 72°	5	85	12
3	toluene	Et*i*-Pr_2N	2.5 : 4 : 7	- 75° → - 5°	28[b]	75	8
4	CH_2Cl_2	*i*-Bu_3N	2.5 : 4 : 7	- 78° → r.t.	27[c]	51	4
5	CH_2Cl_2	*i*-Bu_3N	2.5 : 4 : 9	- 78° → r.t.	27[c]	63	9

Note: a) Determined after oxidation to the aldehyde and reduction with $NaBH_4$ to the corresponding alcohol; b) the reaction did not start until -5°C; c) the reaction did not start until room temperature was reached.

reaction was very slow. The best results, at least in terms of racemization, were obtained using a very hindered tertiary amine, that is *i*-Bu_3N: in this case the oxidation was very slow, but racemization was nearly completely suppressed, although chemical yield were not satisfactory. By increasing the amount of added amine the yields increased, but the degree of racemization was higher as well.

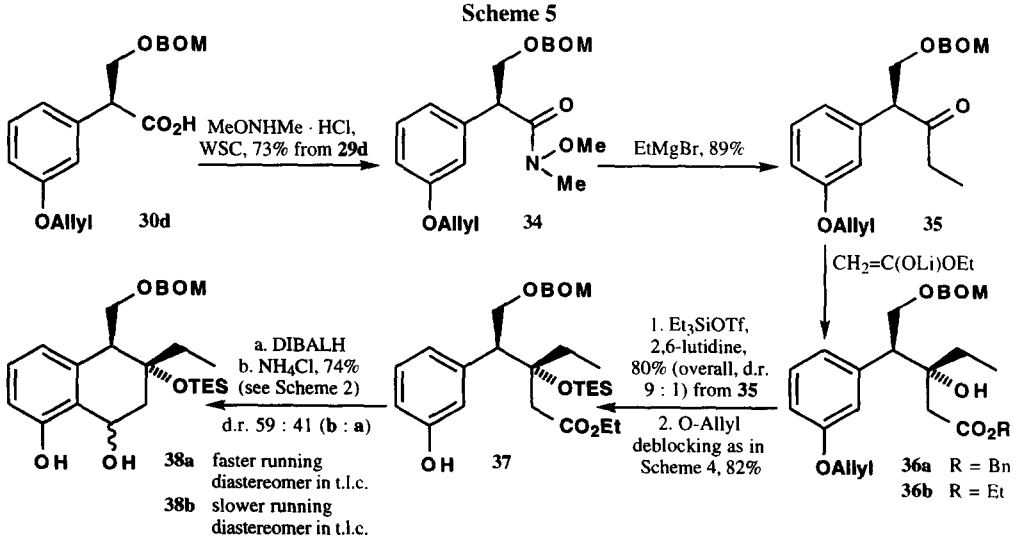
Although the approach to **2**, passing through the aldehyde, seemed in principle more promising, we were not completely satisfied, most of all in terms of chemical yield and of scarce reactivity of the alcohols toward the oxidation. At this point we examined a completely different elaboration of **28**, that is path *b* (Scheme 1). For this purpose we choose benzyloxymethyl ether as protecting group for **28**.[37] Acid **30d**, obtained by Jones oxidation, was transformed into Weinreb hydroxamate **34** (Scheme 5) by condensation with N,O-methyl hydroxylamine in the presence of water soluble carbodiimide (WSC).[38] Hydroxamate **34**, by treatment with EtMgBr, gave in good yield the corresponding ketone **35**.

Moreover, we recently described a very diastereoselective addition of organometallics to 1-alkoxy-2-phenylalkan-3-ones, using Grignards or alkyllithiums reagents as C-nucleophiles.[28] As previously demonstrated on a series of ketones analogues to **35**, this procedure was non-racemizing. As an extension of our previous screening we studied the addition of lithium enolates of esters to **35**. We used either benzyl or ethyl acetate as nucleophiles. Anywhere, we finally preferred the product derived from AcOEt, which was easier to purify.[39] At this level we did not establish the relative configuration of **36**; however, we experienced previously that both the reduction or the organometal addition to similar ketones followed the Felkin-Anh model which matches with the chelation control and so we expected for **36** the relative configuration indicated in Scheme 5.[28]

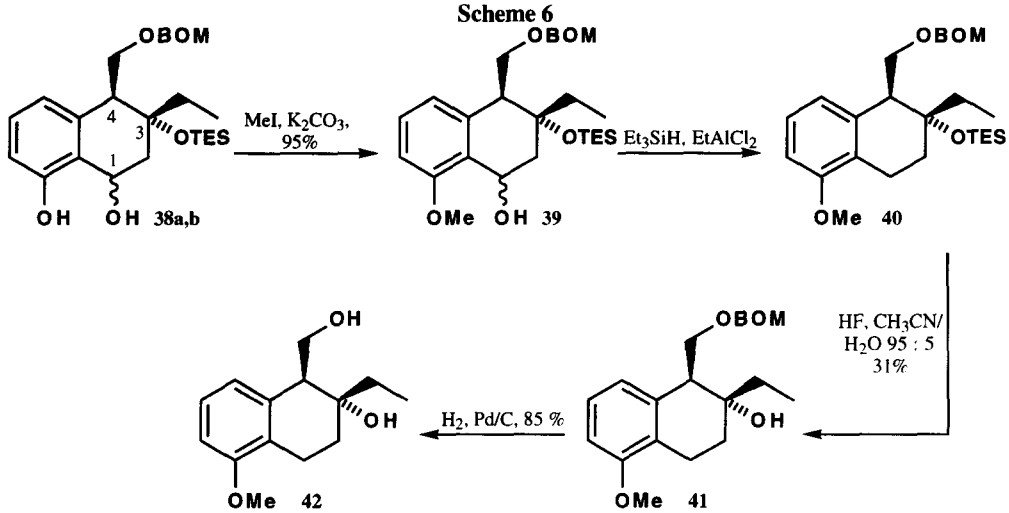
The tertiary alcoholic function, although very unreactive, probably due to steric reasons, was protected as triethylsilyl ether; the final steps of the synthesis followed the usual procedure. The cyclization reaction of **37** furnished a 59 : 41 diastereomeric mixture of **38a,b**, which were in this case easy to separate. Both diastereoisomers were transformed into the corresponding *bis*-Mosher's ester and, from the ^{1}H-n.m.r. analysis of them, we concluded that no racemization had occurred during the whole reaction sequence.

Only at this point we tried to solve the question concerning the relative stereochemistry of chiral centers 3 and 4. Our approach was a chemical correlation with a known intermediate for the synthesis of the AB ring system of Aklavinone, that is tetralin **42**, previously prepared by Meyers.[3c] After the methylation of the phenolic function of **38a,b** (the cyclization diastereomeric mixture was used) we performed a benzylic deoxygenation reaction (Scheme 6). Among a wide screening of methods and reaction conditions,[1b] we found

Scheme 5



Scheme 6



that the best way to obtain **40** is the direct reduction of the alcoholic function using Et_3SiH, although the overall yield was only moderate. Finally, after the deprotection of both the alcoholic functionalities we obtained diol **42**, whose analytical data (^{1}H-n.m.r., ^{13}C-n.m.r., IR, $[\alpha]_D$) resulted identical with the ones reported by Meyers. In this way we confirmed that the addition of an enolate to **35** followed the foreseen Felkin model, in which the aryl group behaves as the large group.

Of course, although **42** is a real intermediate for a four step transformation into **1,** the low yield in the deoxygenation step (**39** → **40**) emphasized that probably this is not the route of choice for the accomplishment of the synthesis. Actually, the crucial deoxygenation step can probably be avoided by using one of the known epimerization procedures for this chiral centre,[3a] thus ensuring a shorter and probably must successful access to **1**.

Anyway, the complexity of our studies illustrates the not trivial chemical behaviour of a series of apparently simple chemicals. For these compounds we frequently had to solve problems connected with a high and sometimes undesired reactivity together with the propensity to undergo racemization processes and, in order to circumvent these problems, we had to study original methodologies.

We wish to thank CNR (Progetto Finalizzato Chimica Fine) and M.U.R.S.T. for financial assistance and Mr Stefano Brusco and Miss Silvia De Vito for their precious collaboration.

EXPERIMENTAL

All n.m.r. were measured in $CDCl_3$ (if not otherwise specified) at 200 MHz (H) or 50 MHz. (C) in ppm (δ scale). Coupling constants are reported in Hertz. Attribution of ^{13}C signals was made also with the aid of DEPT or off resonance experiments. Elemental analyses were performed with a Perkin-Elmer 240 instrument. All reactions employing dry solvents were carried out under a nitrogen atmosphere (if not otherwise specified). T.l.c. analyses were carried out on silica gel plates, which were developed by spraying a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1g) in H_2SO_4 (31 cc) and H_2O (469 cc) and warming. R_f were measured after an elution of 7-9 cm. Chromatographies were carried out on 230-400 mesh silica gel using the "flash" methodology. Petroleum ether (40-60°C) is abbreviated as PE. In extractive work-up aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts, if not otherwise indicated, were finally washed with brine, dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. Porcine pancreatic lipase (PPL) was purchased from Sigma.

Ethyl [3-(methoxymethoxy)phenyl]acetate 8. A solution of **7**[4] (7.08 g, 39.29 mmol) in dry acetonitrile (50 ml) was treated with MOM-Cl (6.71 ml, 78.58 mmol) and triethylamine (10.95 ml, 78.58 mmol) and the

resulting mixture was refluxed for 20 hrs. The reaction was diluted with water and AcOEt and then extracted with AcOEt. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$ and brine. The crude product, obtained after solvent removal, was purified by chromatography using PE : AcOEt 9:1 to give a colourless oil (8.55 g, 97%). R_f 0.38 (PE : AcOEt 9:1). Anal. found C, 64.50%; H, 7.15%. $C_{12}H_{16}O_4$ requires C, 64.27%; H, 7.19%. ^{1}H-n.m.r.: δ 1.26 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 3.48 [3H, s, -OCH_2OCH_3]; 3.59 [2H, s, ArCH_2CO_2Et]; 4.16 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.18 [2H, s, -OCH_2-]; 6.91-6.97 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.20-7.29 [1H, m, *H* meta to -OMOM].

(*d,l*)-Ethyl 3-benzyloxy-2-[3-(methoxymethoxy)phenyl]propanoate 9. A 0.45 M solution of LDA (6.60 ml, 2.97 mmol) in THF : *n*-hexane 75:25 was cooled to -60°C, and treated with a solution of **8** (223 mg, 0.99 mmol) in dry THF (4 ml). After 15 min stirring, BOM-Cl (413 ml, 2.97 mmol) was added *via* syringe and the temperature was allowed to rise to -20°C. After 2 hrs the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were dried over K_2CO_3 in the presence of few drops of triethylamine. After solvent removal under reduced pressure crude **9** was immediately purified by chromatography, using PE : Et_2O : Et_3N 80:20:5. A colourless oil was finally obtained (289 mg, 85%). R_f 0.47 (PE : Et_2O 7:3). Anal. found C, 69.70%; H, 7.10%. $C_{20}H_{24}O_5$ requires C, 69.75%; H,7.02.%. ^{1}H-n.m.r.: δ 1.23 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 3.47 [3H, s, -OCH_2OCH_3]; 3.66 [1H, X part of ABX system, -$CH(CO_2Et)CH_2OBn$]; 3.88 & 4.04 [2H, AB part of ABX system, -CH_2OBn, J_{AB}=9.2, J_{AX} & J_{BX} =8.9, 4.9]; 4.16 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.53 & 4.58 [2H, AB system, -OCH_2Ph, J=12.1]; 5.15 [2H, s, -OCH_2O-]; 6.92 -7.00 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.18-7.38 [6H, m, *H* meta to -OMOM & aromatics of Bn].

(*d,l*)-2-Methoxy-3-[3-(methoxymethoxy)phenyl]propanoic acid 10. Compound **9** (1.87 g, 5.42 mmol) was treated with a solution of potassium hydroxide (365 mg, 6.51 mmol) in MeOH : H_2O 9:1 (15 ml) and the resulting solution was stirred at r. t. for 2 hrs. The mixture was diluted with water and extracted twice with Et_2O. The aqueous layer was treated with 1 N HCl until pH 3, and saturated with NaCl. Extraction with AcOEt, followed by solvent removal gave crude **10**, used as such for the next reaction.

(*d,l*)-Ethyl 5-methoxy-4-[3-(methoxymethoxy)phenyl]-3-oxopentanoate 16. Ester **16** was prepared following the procedure reported in ref. 4 for similar compounds, starting from **10**. Chromatography with PE : Et_2O 7:3 → 6:4 gave **16** as a colourless oil in 40% overall yield. R_f 0.42 (PE : Et_2O 1:1). Anal. found C, 61.70%; H, 7.20%. $C_{16}H_{22}O_6$ requires C, 61.92%; H, 7.15%. ^{1}H-n.m.r.: δ 1.22 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 3.33 [3H, s, >$CH(CH_2OCH_3)$]; 3.40 & 3.47 [2H, AB system, -$COCH_2CO_2$Et, J=15.5]; 3.48 [3H, s, -OCH_2CH_3]; 3.58 [1H, X part of AB system, -$CH(CH_2OCH_3)$-]; 3.99 & 4.10 [2H, AB part of ABX system, >$CH(CH_2OCH_3)$, J_{AB}=8.2, J_{AX} & J_{BX}=8.7, 4.9]; 4.12 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.17 [2H, s, -OCH_2O-]; 6.85-7.02 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.26 [1H, broad t, *H* meta to -OMOM, J=7.9].

(*d,l*)-3-Benzyloxy-2-[3-(methoxymethoxy)phenyl]propan-1-ol 11. A solution of **9** (1.00 g, 2.90 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -78°C and treated with DIBALH (11.6 ml, 1.0 M solution in CH_2Cl_2); the temperature was then allowed to rise to -40°C, before quenching with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O and added with 10 ml of saturated aqueous solution of Rochelle's salt; the biphasic system was vigorously stirred at r. t. until two clear layers were obtained. After extraction with Et_2O and solvent removal, crude **11** was purified by chromatography (PE : Et_2O 8:2 → 4:6), to give a colourless oil (654 mg of **11**, 75%), together with some amounts of the corresponding aldehyde (134 mg, 15%) which can be used together with **11** for the following Jones oxidation. Characterization of **11**: R_f 0.17 (PE : Et_2O 1:1). Anal. found C, 71.60%; H, 7.30%. $C_{18}H_{22}O_4$ requires C, 71.50%; H, 7.33%. ^{1}H-n.m.r.: δ 2.38 [1H, broad s, -*OH*]; 3.19 [1H, centre of m, -$CH(CH_2OBn)CH_2OH$]; 3.48 [3H, s, -OCH_2OCH_3]; 3.75-4.08 [4H, m, -$CH(CH_2OBn)CH_2OH$]; 4.56 [2H, s, -OCH_2Ph]; 5.16 [2H, s, -OCH_2O-]; 6.84-6.98 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.19-7.38 [6H, m, *H* meta to -OMOM & aromatics of Bn]. Characterization of the aldehyde: **3-Benzyloxy-2-[3-(methoxymethoxy)phenyl]propanal**. R_f 0.53 (PE : Et_2O 1:1). ^{1}H-n.m.r.: δ 3.47 [3H, s, -OCH_2OCH_3]; 3.76-3.87 [2H, m, Ar$CH(CH_2OBn)$-]; 4.07-4.15 [1H, m, Ar$CH(CH_2OBn)CHO$]; 4.54 [2H, s, -OCH_2Ph]; 5.16 [2H, s, -OCH_2O-]; 6.84-7.02 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.20-7.40 [6H, m, *H* meta to -OMOM & aromatics of Bn]; 9.76 [1H, d, -*CHO*, J=1.9].

(*d,l*)-3-Benzyloxy-2-[3-(methoxymethoxy)phenyl]propanoic acid 12. A solution of alcohol **11** (303 mg, 1.00 mmol) in dry acetone (12 ml) was cooled to 0°C and treated dropwise with Jones reagent (prepared from 10 g CrO_3, 8.6 ml of 96% H_2SO_4, 14 ml of H_2O, and brought up to 40 ml)[40] until complete reaction [about 40 drops (from a Pasteur pipette)/mmol of substrate usually needed]. After about 1.5 hrs, 5% aqueous solution of $NH_4H_2PO_4$ was added to adjust the pH to 3. The mixture was saturated with brine and extracted with AcOEt. The organic extracts were washed with saturated brine containing 10% Na_2SO_3 solution and the solvent removed *in vacuo*. Chromatography with AcOEt, containing 1% of acetic acid gave the corresponding acid (259 mg, 82%) as a white solid. ^{1}H-n.m.r.: δ 3.46 [3H, s, -OCH$_2$OC*H*$_3$]; 3.67 [1H, X part of ABX system, -C*H*(CH$_2$OBn)CO$_2$H]; 3.90 & 4.03 [2H, AB part of ABX system, -CH(C*H*$_2$OBn)CO$_2$H, J_{AB}=9.0, J_{AX} & J_{BX}=9.0, 4.4]; 4.53 & 4.58 [2H, AB system, -OC*H*$_2$Ph, J=12.2]; 5.15 [2H, s, -OC*H*$_2$O-]; 6.92-6.99 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.19-7.30 [6H, m, *H* meta to -OMOM & aromatics of Bn]; 9.35 [1H, broad s, -CO$_2$*H*].

(*d,l*)-Ethyl 5-benzyloxy-4-[3-(methoxymethoxy)phenyl]-3-oxopentanoate 14. The homologation reaction was performed as described in ref. 4 for similar compounds, starting from **12**. Chromatography with PE : AcOEt 9:1 → 8:2 gave **14** in 55% overall yield as a colourless oil. R_f 0.55 (PE : Et$_2$O 1:1). Anal. found C, 68.50%; H, 6.75%. $C_{22}H_{26}O_6$ requires C, 68.38%; H, 6.78%. ^{1}H-n.m.r.: δ 1.20 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.1]; 3.42 & 3.48 [2H, AB system, -COC*H*$_2$CO$_2$Et, J=15.5]; 3.47 [3H, s, -OCH$_2$C*H*$_3$]; 3.65 [1H, X part of AB system, -C*H*(CH$_2$OBn)-]; 4.08 & 4.14 [2H, AB part of ABX system, >CH(C*H*$_2$OBn), J_{AB}=8.2, J_{AX} & J_{BX}=8.5, 3.9]; 4.11 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.1]; 4.47 & 4.54 [2H, AB system, -CH$_2$OC*H*$_2$Ph, J=12.1]; 5.15 [2H, s, -OC*H*$_2$O-]; 6.83-7.01 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.21-7.38 [6H, m, *H* meta to -OMOM & aromatics of Bn].

(*d,l*)-Ethyl 5-benzyloxy-4-(3-hydroxyphenyl)-3-oxopentanoate 15. A solution of **14** (312 mg, 0.81 mmol) in dry CH_2Cl_2 (6 ml) was treated with ethanedithiol (68 µl, 0.81 mmol) and $BF_3{\cdot}Et_2O$ (100 µl, 0.81 mmol). After just 5 min the solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O. Solvent was removed *in vacuo* and crude **15** chromatographed with PE : Et$_2$O 1:1 to give pure **15** as a pale yellow oil (244 mg, 88%). R_f 0.50 (PE : Et$_2$O 4:6). Anal. found C, 70.25%; H, 6.50%. $C_{20}H_{22}O_5$ requires C, 70.16%; H, 6.48%. ^{1}H-n.m.r.: δ 1.20 [3H, t, -CO$_2$C H$_2$C*H*$_3$, J=7.1]; 3.42 & 3.48 [2H, AB system, -COC*H*$_2$CO$_2$Et, J=15.6]; 3.64 [1H, centre of m, -C*H*(CH$_2$OBn)-]; 3.98-4.18 [2H, m, -CH(C*H*$_2$OBn)-]; 4.11 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.1]; 4.47 & 4.53 [2H, AB system, -OC*H*$_2$Ph, J=12.1]; 5.37 [1H, broad s, -O*H*]; 6.67-6.80 [3H, m, *H* para & 2 *H* ortho to -OH]; 7.19 [1H, t, *H* meta to -OH, J=7.8,]; 7.25-7.38 [5H, m, aromatics of Bn].

(*d,l*)-Ethyl 5-benzyloxy-3,3-ethylendithio-4-(3-hydroxyphenyl)pentanoate 17. A solution of ethanedithiol (520 µl, 6.18 mmol) in dry THF (1.51 ml, 18.60 mmol) and CH_2Cl_2 (5 ml) was treated with trimethylsilyltriflate (2.88 ml, 14.88 mmol) and stirred at r. t. for 5 min. The resulting solution was transferred dropwise, *via* syringe, into a flask containing a solution of **15**, previously cooled to 0°C. After 5 min the solution was stirred at r. t. overnight. After dilution with saturated aqueous $NaHCO_3$, the reaction was extracted with Et_2O and, after solvent removal, chromatography with PE : Et$_2$O 6:4 → 1:1 furnished **17** as a colourless oil (394 mg, 76%). R_f 0.34 (PE : Et$_2$O 1:1). Anal. found C, 63.00%; H, 6.30%. $C_{22}H_{26}O_4S_2$ requires C, 63.13%; H, 6.26%. ^{1}H-n.m.r.: δ 1.22 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.1]; 2.87 & 3.04 [2H, AB system, -C*H*$_2$CO$_2$Et, J=17.0]; 2.96-3.30 [4H, m, -S(C*H*$_2$)$_2$S-]; 3.94-4.26 [3H, m, -C*H*(CH$_2$OBn)-]; 4.11 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.1]; 4.43 & 4.51 [2H, AB system, -OC*H*$_2$Ph, J=12.2]; 4.97 [1H, broad s, -O*H*]; 6.73 [1H, broad dd, *H* ortho to -OH & para to the side chain, J=7.8, 2.5]; 6.87 [1H, t, *H* ortho to both substituents, J=2.0]; 6.96 [1H, broad d, *H* para to -OH, J=7.8]; 7.15 [1H, t, *H* meta to -OH, J=7.8]; 7.16-7.36 [5H, m, aromatics of Bn]. ^{13}C-n.m.r.: δ 14.29 [-OCH$_2$*C*H$_3$]; 39.92 [2C, -S*C*H$_2$*C*H$_2$S-]; 49.39 [-*C*H$_2$CO$_2$Et]; 52.64 [Ar*C*HCH$_2$OBn)-]; 60.61 [-O*C*H$_2$CH$_3$]; 69.25 [>*C*(SCH$_2$CH$_2$S)]; 72.75 & 72.85 [ArCH(*C*H$_2$O*C*H$_2$Ph)-]; 114.23 [*C*H ortho to -OH & para to the side chain]; 116.44 [*C*H ortho to both substituents]; 121.51 [*C*H para of -OH]; 127.25 [Ar*C* para to Bn]; 127.41 & 128.06 [4C, Ar*C* ortho & meta of Bn]; 129.04 [*C*H meta to -OH]; 138.04 [Ar*C ipso* of Bn]; 141.71 [*C* meta to -OH]; 155.30 [*C*OH of aryl]; 170.35 [>*C*O].

(*d,l*)-Ethyl 5-methoxy-3,3-ethylendithio-4-[3-[(hydroxy)phenyl]pentanoate 18. It was prepared starting from **16**, following the procedure employed for conversion of **15** into **17**; in this case, both deprotection of

MOM & thioketalization took place. Chromatography with PE : Et_2O 6:4 → 1:1 furnished **18** as a colourless oil in 70% overall yield. R_f 0.31 (PE : Et_2O 1:1). Anal. found C, 55.95%; H, 6.50%. $C_{16}H_{22}O_4S_2$ requires C, 56.11%; H, 6.47%. ^{1}H-n.m.r.: δ 1.26 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 2.83 & 2.98 [2H, AB system, -CH_2CO_2Et, J=17.2]; 3.08-3.25 [5H, m, -S(CH_2)$_2$S- & ArCH(CH_2OMe)-]; 3.29 [3H, s, -CH_2OCH_3]; 3.94-4.21 [2H, m, -CH(CH_2OMe)-]; 4.15 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.94 [1H, broad s, -OH]; 6.72 [1H, ddd, H ortho to -OH & para to the side chain, J=8.1, 2.6, 0.9]; 6.88 [1H, t, H ortho to both substituents, J=2.0]; 6.96 [1H, broad dt, H para to -OH, J=7.8, 1.2]; 7.16 [1H, t, H meta to -OH, J=7.8]. ^{13}C-n.m.r.: δ 14.34 [-OCH_2CH_3]; 39.95 & 40.04 [2C, -SCH_2CH_2S-]; 49.41 [-CH_2CO_2Et]; 52.43 [ArCH(CH_2OCH_3)-]; 58.74 [-OCH_3]; 60.60 [-OCH_2CH_3]; 69.25 [>C(SCH_2CH_2S)]; 75.35 [-CH_2OCH_3]; 114.38 & 116.37 [2CH ortho to -OH]; 121.24 [CH para to -OH]; 129.17 [CH meta to -OH]; 141.56 [C meta to -OH]; 155.46 [C-OH of aryl]; 170.23 [>CO].

4-(Benzyloxymethyl)-3,3-ethylendithio-1,2,3,4-tetrahydronaphthalene-1,8-diol 19. The general procedure reported in ref. 4 was followed. Chromatography with PE : Et_2O 1:1 yielded 69% of a mixture of diastereomers [d.r. 53 : 47] as a colourless oil. The two diastereomers, although slightly separated in t.l.c. [R_f 0.39 & 0.42 (PE : Et_2O 4:6) respectively] were not separated and reported spectroscopic data were collected on the diastereomeric mixture. ^{1}H-n.m.r.: δ 2.48 [1H, d, >C(1)OH- (diast. B), J=10.2]; 2.57 [1H, broad d, H_2 (diast. A), J=15.2]; 2.73 [2H, d, H_2 (diast B), J=7.3]; 3.03 [1H, dd, H_2, (diast. A), J=15.2, 7.3]; 3.25-3.50 [5H + 5H, m, -SCH_2CH_2- + H_4 (diast. A & B)]; 3.73 [2H, apparent d, ArCH(R)CH_2OBn (diast. A or B), J=4.9]; 3.86 [1H, d, >C(1)OH- (diast. A), J=11.8]; 3.90 & 4.03 [2H, AB part of ABX system, ArCH(R)CH_2OBn (diast. A or B), J_{AB}=10.0, J_{AX} & J_{BX}=4.4, 3.6]; 4.39 & 4.46 [2H, AB system, -OCH_2Ph (diast. A or B), J=12.5]; 4.32 & 4.48 [2H, AB system, -OCH_2Ph (diast. A or B), J=11.7]; 4.92 [1H, dd, H_1 (diast. A), J=12.1, 7.0]; 5.09 [1H, broad dt, H_1 (diast. B), J=10.5, 7.4]; 6.85-7.40 [8H + 8H, m, H_5 + H_6 + H_7 + aromatics of Bn (diast. A & B)]; 7.57 & 7.68 [1H + 1H, 2 s, >C(8)OH- (diast. A & B)].

1,8-Diacetoxy-4-(benzyloxymethyl)-3,3-ethylendithio-1,2,3,4-tetrahydronaphthalene 20. For the acetylation reaction, crude **19** was used and the reaction was performed as described in ref. 4 on similar compounds. Chromatography (PE : Et_2O 1:)1 gave **20** in 62% yield from **17** as a mixture of diastereomers [d.r. 53 : 47]. The two diastereomers are not separated in t.l.c. and the reported spectroscopic data were collected on the diastereomeric mixture. R_f 0.39 (PE : Et_2O 1:1). ^{1}H-n.m.r.: δ 2.01 & 2.07 [3H + 3H, 2 s, >C(1)OCOCH_3- (diast. A & B)]; 2.23 & 2.24 [3H + 3H, 2 s, >C(8)OCOCH_3- (diast. A & B)]; 2.42 [1H, dd, H_2 (diast. A), J=14.0, 6.8]; 2.42 [1H, dd, H_2 (diast. B), J=15.0, 2.4]; 2.95 [1H, ddd, H_2, (diast. A), J=14.0, 8.5, 1.8]; 3.10 [2H, dd, H_2, (diast. B), J=15.0, 6.0]; 3.20-3.40 [5H + 5H, m, -SCH_2CH_2S- (diast. A & B) + H_4 (diast. A & B)]; 3.81 & 3.96 [2H, AB part of ABX system, ArCH(R)CH_2OBn (diast. A or B), J_{AB}=9.6, J_{AX} & J_{BX}=6.7, 4.9]; 3.88-3.91 [2H, m, ArCH(R)CH_2OBn (diast. A or B)]; 4.36 & 4.39 [2H, AB system, -OCH_2Ph (diast. A or B), J=10.4]; 4.42 & 4.49 [2H, AB system, -OCH_2Ph (diast. A or B), J=11.8]; 6.18 [1H, dd, H_1 (diast. B), J=5.9, 2.4]; 6.25 [1H, dd, H_1 (diast. A), J=8.5, 6.8]; 7.00-7.37 [8H + 8H, m, H_5 + H_6 + H_7 + aromatics of Bn (diast. A or B)]. ^{13}C-n.m.r.: δ 20.92 (2C), 20.98 (1C) & 21.20 [(1C), >C(1)OCOCH_3- & >C(8)OCOCH_3- (diast. A & B)]; 38.43 (1C), 39.10 (2C) & 39.50 [(1C), -SCH_2CH_2S- (diast. A & B)]; 41.86 & 42.29 [2C, C_2 (diast. A & B)]; 52.30 & 52.62 [2C, C_4 (diast. A & B)]; 65.44 & 66.55 [2C, C_1 (diast. A & B)]; 66.87 & 68.37 [2C, C_3 (diast. A & B)]; 73.05 & 73.12 [2C, -CH_2OCH_2Ph (diast. A & B)]; 74.56 & 74.72 [2C, -CH_2OBn (diast. A & B)]; 121.26 & 121.79 [2C, C_7 (diast. A & B)]; 125.20 & 125.46 [2C, C_{8a} (diast. A & B)]; 126.79 & 127.21 [2C, C_5 (diast. A & B)]; 127.32 & 127.43 [2C, ArC para of Bn (diast. A & B)]; 127.43 & 127.46 [4C, ArC meta of Bn (diast. A & B)]; 128.26 [4C, ArC ortho of Bn (diast. A & B)]; 128.97 & 129.13 [2C, C_6 (diast. A & B)]; 138.01 & 138.06 [2C, ArC *ipso* of Bn (diast. A & B)]; 141.20 & 142.05 [2C, C_{4a} (diast. A & B)]; 149.52 & 149.97 [2C, C_8 (diast. A & B)]; 168.96, 168.99, 170.18 & 170.26 [4C, >C(1)(OCOCH$_3$)- & >C(8)(OCOCH$_3$)- (diast. A & B)].

3,3-Ethylendithio-4-(methoxymethyl)-1,2,3,4-tetrahydronaphthalene-1,8-diol 21. The general procedure reported in ref. 4 was followed. Chromatography with PE : Et_2O 1:1 yielded 67% of a mixture of diastereomers [d.r. about 1 : 1] as a colourless oil. The two diastereomers are not separated in t.l.c.; so, the reported spectroscopic data were collected on the diastereomeric mixture. R_f 0.27 (PE : Et_2O 1:1). ^{1}H-n.m.r.: (assignments were performed working on two different samples, one slightly enriched in diastereomer A, the

other one slightly enriched in diastereomer B). Diast. A: δ 2.73 [1H, d, H_2, J=7.1]; 2.88 [1H, d, >C(1)O*H*-, J=10.2]; 3.21-3.39 [9H, m, -OCH_3 + -SCH_2CH_2S- + H_2 + H_4]; 3.84-3.86 [2H, m, -CH_2OCH$_3$]; 5.12 [1H, dt, H_1, J=10.2, 7.1]; 6.85 [2H, centre of m, H_5 + H_7]; 7.19 [1H, t, H_6, J=8.0]; 7.66 [1H, s, >C(8)O*H*-]. Diast. B: δ 2.58 [1H, dt, H_2, J=15.0, 1.4]; 3.01-3.44 [6H, m, -SCH_2CH_2S- + H_2 + H_4]; 3.27 [3H, s, -OCH_3]; 3.62 & 3.67 [2H, AB part of ABX system, -CH_2OCH$_3$, J_{AB}=6.9, J_{AX} & J_{BX}=5.5, 5.2]; 3.87 [1H, d, >C(1)O*H*-, J=11.7]; 4.95 [1H, dd, H_1, J=14.0, 10.8]; 6.79-6.86 [2H, m, H_5 + H_7]; 7.16 [1H, t, H_6, J=7.8]; 7.57 [1H, s, >C(8)O*H*-].

1,8-Diacetoxy-3,3-ethylendithio-4-(methoxymethyl)-1,2,3,4-tetrahydronaphthalene 22. For the acetylation reaction, crude **21** was used and the reaction was performed as described in ref. 4. Chromatography with PE : Et_2O 1:1 gave **22** in 67% overall yield from **18** as a mixture of diastereomers [d.r. about 1 : 1]. The two diastereomers are not separated in t.l.c. and the reported spectroscopic data were collected on the diastereomeric mixture. R_f 0.43 (PE : Et_2O 1:1). ^{1}H-n.m.r.: δ 2.06 & 2.07 [3H + 3 H, 2 s, >C(1)(OCOCH_3)- (diast. A & B)]; 2.23 [3H + 3H, 2 s, >C(8)(OCOCH_3)- (diast. A & B)]; 2.34-2.44 [1H, m, H_2 (diast. A or B)]; 2.90-3.09 [1H, m, H_2 (diast. A or B)]; 3.23 & 3.34 [3H + 3H, 2 s, -OCH_3 (diast. A & B)]; 3.23-3.39 [4H + 4H, m, -SCH_2CH_2S- (diast. A & B)]; 3.63-3.92 [3H + 3H, m, ArCH(R)CH_2OBn + H_4 (diast. A & B]; 6.26 [1H, dd, H_1 (diast. A or B), J=8.5, 7.0]; 6.39 [1H, dd, H_1 (diast. A or B), J=6.0, 2.5]; 7.00-7.40 [3H + 3H, m, H_5 + H_6 + H_7 (diast. A & B)]. ^{13}C-n.m.r.: δ 20.81 (2C), 20.93 (1C) & 21.08 [(1C), >C(1)(OCOCH_3)- & >C(8)(OCOCH_3)- (diast. A & B)]; 38.38, 39.00, 39.08 & 39.39 [4C, -SCH_2CH_2S- (diast. A & B)]; 42.10 & 42.26 [2C, C_2 (diast. A & B)]; 51.98 & 52.45 [2C, C_4 (diast. A & B)]; 65.45 & 66.50 [2C, C_1 (diast. A & B)]; 66.91 & 68.26 [2C, C_3 (diast. A & B)]; 76.99 [2C, -CH_2OCH$_3$ (diast. A & B)]; 55.85 & 58.80 [2C, -OCH_3 (diast. A & B)]; 121.17 & 121.67 [2C, C_7 (diast. A & B)]; 125.08 & 125.25 [2C, C_{8a} (diast. A & B)]; 126.58 & 127.14 [2C, C_5 (diast. A & B)]; 128.88 & 129.04 [2C, C_6 (diast. A & B)]; 141.46 & 142.04 [2C, C_{4a} (diast. A & B)]; 149.47 & 149.95 [2C, C_8 (diast. A & B)]; 168.79, 168.83, 170.05 & 170.12 [4C, >C(1)(OC*O*CH$_3$)- & >C(8)(OC*O*CH$_3$)- (diast. A & B)].

2-[3-(Allyloxy)phenyl]-1,3-diacetoxypropane 26. A solution of **24**[17b] (626 mg, 3.01 mmol) in dry pyridine (5 ml) was treated with acetic anhydride (850 μl, 9.02 mmol). After 6 hrs stirring at r. t. the solvent was removed under reduced pressure. The residue was taken up with water and Et_2O and the pH was adjusted to 1-2 by careful addition of 1 N HCl. The mixture was then extracted with Et_2O. The organic layers were washed until neutral with a $NaHCO_3$ solution and water, and the solvent was removed. Chromatography with PE : Et_2O 6:4 gave **26** as a pale yellow oil (808 mg, 92%). R_f 0.36 (PE : Et_2O 6:4). Anal. found C, 65.65%; H, 6.95%. $C_{16}H_{20}O_5$ requires C, 65.74%; H, 6.90%. ^{1}H-n.m.r.: δ 2.03 [6H, s, -CH(CH$_2$OCOCH_3)$_2$]; 3.28 [1H, quintuplet, -C*H*(CH$_2$OAc)$_2$, J=6.6]; 4.32 [4H, d, -CH(CH_2OAc)$_2$, J=6.6]; 4.53 [2H, dt, -CH_2-CH=CH$_2$, J=5.3, 1.5]; 5.30 [1H, dq, -CH=CH*H trans* to -CH$_2$-, J=10.4, 1.5]; 5.42 [1H, dq, -CH=CH*H cis* to -CH$_2$-, J=17.3, 1.5]; 6.07 [1H, ddt, -CH$_2$-C*H*=CH$_2$, J=17.3, 10.4, 5.3]; 6.80-6.88 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.19-7.30 [1H, m, *H* meta to -OAllyl].

(*S*)-3-Acetoxy-2-[3-(allyloxy)phenyl]propan-1-ol 28. Diacetate **26** (3.20 g, 10.95 mmol) was dissolved in diisopropylether (15 ml, 16.3%); a pH 7 buffer solution (KH_2PO_4/Na_2HPO_4 0.02 M, 77 ml, 83.7%) was added, followed by crude PPL (3.30 g) and the resulting two-layer system was stirred at 18-20°C, while pH was maintained at 7 by continuous addition of aqueous 1 N NaOH from an automatic burette. After consumption of 13.28 mmol of NaOH (24.5 hrs required) the mixture was diluted with brine and the catalyst was filtered on celite. After saturation with NaCl the extraction was performed with AcOEt (trice) and with AcOEt : MeOH 9:1 (twice) to give, after solvent removal, crude monoacetate. Chromatography with PE : Et_2O 7:3 → 3:7 and finally with AcOEt furnished monoacetate **28** as a colourless oil (1.80 g, 66%) together with some diol **24** (433 mg, 19%). Conversion (determined by ^{1}H-n.m.r. analysis of crude mixture): 58.9%. Enantiomeric excess [determined by ^{1}H-n.m.r. analysis in the presence of Eu(hfc)$_3$]: 95%. For other characterizations see ref. 17b. $[\alpha]_D$ = - 12.0° (c 2.17, $CHCl_3$).

(*R*)-3-Acetoxy-2-[3-(allyloxy)phenyl]propan-1-ol *ent*-28. This compound was prepared following procedure reported in ref. 17b, starting from diol **24**. $[\alpha]_D$ = + 11.5° (c 2.00, $CHCl_3$).

(*R*)-2-[3-(Allyloxy)phenyl]-3-(*t*-butyldiphenylsilyloxymethyl)propan-1-ol 29a. a) A solution of **28** (251 mg, 1.00 mmol) in dry DMF (3 ml) was treated with *t*-BuPh$_2$SiCl (442 μl, 1.7 mmol) and imidazole (136 mg,

2.00 mmol) and stirred for 2 hrs at r. t.. The solution was diluted with water and extracted with PE : Et_2O 1:1. Combined organic extracts were washed with water and brine and finally concentrated *in vacuo* to give **(*R*)-3-acetoxy-2-[3-(allyloxy)phenyl]-2-[(*t*-butyldiphenylsilyl)oxy]propane** as a pale yellow oil used as such in the next reaction. R_f 0.46 (PE : Et_2O 85:15). **b**) **29a** was prepared following the general procedure for hydrolysis of acetyl group reported below in 95% overall yield from **28**. R_f 0.35 (PE : Et_2O 65:35). Anal. found C, 72.45%; H, 8.55%. $C_{28}H_{34}O_3Si$ requires C, 72.32%; H, 8.6%. $[\alpha]_D$ = + 8.9° (c 2.00, $CHCl_3$). ^{1}H-n.m.r.: δ 1.08 [9H, s, *t*Bu-]; 2.36 [1H, broad t, -O*H*, J=5.5]; 3.09 [1H, centre of m, ArC*H*<]; 3.83-3.99 [3H, m, -C*H*HOH + -CH_2OTBDPS]; 4.05-4.16 [1H, m, -CH*H*OH]; 4.47 [2H, dt, -OCH_2CH=CH_2, J=5.3, 1.5]; 5.27 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.5, 1.4]; 5.38 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.2, 1.6]; 6.03 [1H, ddt, -OCH_2C*H*=CH_2, J=17.3, 10.5, 5.3]; 6.71-6.80 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.18 [1H, broad t, *H* meta to -OAllyl, J=7.8] 7.32-7.45 [6H, m, *H* meta & para of -Si*Ph*$_2$*t*Bu]; 7.60-7.66 [4H, m, *H* ortho of -Si*Ph*$_2$*t* Bu].

General procedure for hydrolysis of acetyl group. Crude mono-O-acetyl, mono-O-protected 1,3-[2-(3-allyloxy)phenyl]propanediols (10 mmol) were dissolved in dry MeOH (60 ml), cooled to 0°C and treated with KOH (16 ml of 1N solution in MeOH). After stirring 1-2 hrs at 0°C the mixture was neutralized by addition of $NH_4H_2PO_4$ (5% solution in water) and concentrated *in vacuo*. The residue was diluted with water and extracted with Et_2O. After solvent removal, chromatography (PE : Et_2O 7:3 → Et_2O) gave pure products as colourless oils.

(*R*)-2-[3-(Allyloxy)phenyl]-3-[(4-methoxybenzyl)oxy]propan-1-ol 29b. a) **(*S*)-3-Acetoxy-2-[3-(allyloxy)phenyl]-2-[(4-methoxybenzyl)oxy]propane**. 4-Methoxybenzyl trichloroacetimidate was prepared on a multigram scale and distilled;[41] after purification it showed the following ^{1}H-n.m.r. spectrum: δ 3.82 [3H, s, -COC*H*$_3$]; 5.28 [2H, s, ArC*H*$_2$-]; 6.88-7.40 [4H, m, aromatics]; 8.36 [1H, s, >NH]. Reaction: monoacetate **28** (1.27 g, 5.07 mmol) was dissolved in dry $CHCl_3$ (20 ml) and treated with camphorsulfonic acid (118 mg, 0.51 mmol) and 30 mg of powdered 4 Å molecular sieves. The flask was equipped with an addition funnel, used to add portionwise (8 additions required; each addition was done every 30 min) a solution of 4-methoxybenzyl trichloroacetimidate (2.06 ml, 10.15 mmol) in dry $CHCl_3$ (15 ml). The resulting solution was stirred at r. t. for one day; then it was diluted with water, neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O. After solvent removal, chromatography with PE : Et_2O 8:2 → 6:4 gave protected alcohol as a colourless oil (1.45 g, 77%). R_f 0.38 (PE : Et_2O 6:4). ^{1}H-n.m.r.: δ 1.97 [3H, s, -OCOC*H*$_3$]; 3.21 [1H, quintuplet, ArC*H*<, J=4.7]; 3.65 [2H, d, -CH_2OMPM, J=6.4]; 3.80 [3H, s, -OC*H*$_3$]; 4.32 & 4.38 [2H, AB part of ABX system, -CH_2OAc, J_{AB}=11.0, J_{AX} & J_{BX}=6.8, 6.3]; 4.43 [2H, s, -C*H*$_2$(4-OMe)Ph]; 4.51 [2H, dt, -OCH_2CH=CH_2, J=5.2, 1.4]; 5.28 [1H, dq, -OCH$_2$CH=C*H*H *trans* to -CH_2-, J=10.4, 1.4]; 5.40 [1H, dq, -OCH$_2$CH=C*H*H *cis* to -CH_2-, J=17.3, 1.6]; 6.05 [1H, ddt, -OCH$_2$C*H*=CH_2, J=17.2, 10.5, 5.3]; 6.77-6.94 [5H, m, aromatics]; 7.10-7.30 [3H, m, aromatics]. **b**) **29b** was prepared following the general procedure for hydrolysis of acetyl group reported above in 82% yield from the corresponding acetate. Chromatography PE : Et_2O 45:55 → 3:7. R_f 0.29 (PE : Et_2O 1:1). Anal. found C, 73.00%; H, 7.40%. $C_{20}H_{24}O_4$ requires C, 73.15%; H, 7.37%. $[\alpha]_D$ = + 16.7° (c 1.80, $CHCl_3$). ^{1}H-n.m.r.: δ 2.34 [1H, broad s, -O*H*]; 3.16 [1H, centre of m, ArC*H*<]; 3.69-4.02 [4H, m, -CH_2OH + -CH_2OMPM]; 3.81 [3H, s, -OC*H*$_3$]; 4.48 [2H, s, -OC*H*$_2$[(4-OMe)Ph]]; 4.51 [2H, dt, -OCH_2CH=CH_2, J=5.4, 1.5]; 5.28 [1H, dq, -OCH$_2$CH=C*H*H *trans* to -CH_2-, J=10.5, 1.4]; 5.40 [1H, dq, -OCH$_2$CH=C*H*H *cis* to -CH_2-, J=17.3, 1.6]; 6.05 [1H, ddt, -OCH$_2$C*H*=CH_2, J=17.3, 10.5, 5.3]; 6.78-6.91 [5H, m, aromatics]; 7.15-7.23 [3H, m, aromatics].

(*R*)-2-[3-(Allyloxy)phenyl]-3-(benzyloxy)propan-1-ol 29c. a) **(*R*)-1-Acetoxy-2-[3-(allyloxy)phenyl]-3-[(tetrahydropyran-2-yl)oxy]propane.** A solution of ***ent*-28** (1.27 g, 5.09 mmol) in dry CH_2Cl_2(12 ml) was cooled to 0°C and treated with 3,4-dihydro-2*H*-pyran (1.40 ml, 15.3 mmol) and *p*-toluenesulfonic acid (0.5 ml of a 0.1 M solution in THF) and stirred at the same temperature for 1 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with Et_2O to give, after solvent removal, a pale yellow oil used as such in the next reaction R_f 0.36 (PE : Et_2O 65:35) **b**) **(*S*)-2-[3-(Allyloxy)phenyl]-3-[(tetrahydropyran-2-yl)oxy]propan-1-ol.** This compound was prepared following the general procedure for hydrolysis of acetyl group reported above. Chromatography PE : Et_2O 45:55 → 35:65. Yield 98% from ***ent*-28**. R_f 0.30 (PE : Et_2O 4:6). $[\alpha]_D$ = - 14.5° (c 1.18, $CHCl_3$). This compound was also prepared in four steps (84% yield) from **(*S*)-28**

of 95% e.e. (see ref. 1a). In this case $[\alpha]_D$= -15.3°(c 1.2, $CHCl_3$). ^{1}H-n.m.r.: δ 1.40-1.80 [6H, m, -$CH_2CH_2CH_2CH_2O$- of THP]; 2.49-2.61 [1H, m, -*OH*]; 3.03-3.20 [1H, m, ArC*H*<]; 3.41-4.12 [6H, m, -CH_2OH + -CH_2OTHP + -OCH_2- of THP]; 4.53 [2H, dt, -$OCH_2CH{=}CH_2$, J=5.3, 1.5]; 4.61 [1H, centre of m, -OC*H*O- of THP]; 5.29 [1H, dq, -$OCH_2CH{=}CHH$ *trans* to -CH_2-, J=10.5, 1.4]; 5.41 [1H, dq, -$OCH_2CH{=}CHH$ *cis* to -CH_2-, J=17.3, 1.6]; 6.06 [1H, ddt, -$OCH_2CH{=}CH_2$, J=17.3, 10.6, 5.3]; 6.75-6.87 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.22 [1H, t, *H* meta to -OAllyl, J=8.1]. **c) (*S*)-2-[3-(Allyloxy)phenyl]-3-benzyloxy-2-[(tetrahydropyran-2-yl)oxy]propane.** The above prepared alcohol (1.45 g, 4.96 mmol) was dissolved in dry DMF (25 ml) and cooled to 0°C; it was treated with benzyl bromide (892 µl, 7.50 mmol) and NaH (348 mg, 7.50 mmol, 51.7% suspension in mineral oil). After 4 hrs at 0°C the thick solution was stirred 1 h at 10°C and 1 h at r. t.. The mixture was diluted with $NH_4H_2PO_4$ (5% in H_2O) and extracted with Et_2O. Combined organic extracts were washed with water and brine and concentrated *in vacuo*. Chromatography PE : Et_2O 9:1 → 8:2 gave the desired product as a colourless oil (1.76 g, 93%). R_f 0.48 (PE : Et_2O 75:25). $[\alpha]_D$ = + 5.2° (c 2.08, $CHCl_3$). ^{1}H-n.m.r.: δ 1.40-1.75 [6H, m, -$CH_2CH_2CH_2CH_2O$- of THP]; 3.17 [1H, q, ArC*H*<, J=6.3]; 3.39-3.49 [1H, m, -OCHOC*H*H- of THP]; 3.58-3.85 [4H, m, -CH_2OBn + -*H*CHOTHP + -OCHOCH*H*- of THP]; 4.44-4.54 [4H, m, -$OCH_2CH{=}CH_2$ + -CH_2Ph]; 3.94-4.04 [1H, m, -*H*CHOTHP]; 4.56 [1H, centre of m, -OC*H*O- of THP]; 5.27 [1H, dq, -$OCH_2CH{=}CHH$ *trans* to -CH_2-, J=10.3, 1.4]; 5.40 [1H, dq, $OCH_2CH{=}CHH$ *cis* to -CH_2-, J=17.3, 1.6]; 6.05 [1H, ddt, -$OCH_2CH{=}CH_2$, J=17.3, 10.5, 5.3]; 6.78 [1H, broad ddd, *H* para to-OAllyl, J=8.1, 2.5, 1.1]; 6.86-6.89 [2H, m, 2*H* ortho to -OAllyl]; 7.20 [1H, t, *H* meta to --OAllyl, J=8.1]; 7.26-7.31 [5H, aromatics of -CH_2Ph]. **d)** The monobenzylether above prepared was dissolved in dry MeOH (35 ml), cooled to 0°C and treated with *p*-toluenesulfonic acid (41 mg, 213 µmol). After 1 h the solution was allowed to react for 2 hrs at 10°C and 2 hrs at r. t.. The mixture was neutralized by addition of saturated aqueous $NaHCO_3$ and concentrated *o*. The residue was diluted with water and extracted with AcOEt. After solvent removal, chromatography PE : Et_2O 6:4 → 1:1 gave pure **29c** as a colourless oil (1.25 g, 98%). R_f 0.34 (PE : Et_2O 1:1). Anal. found C, 76.65%; H, 7.35%. $C_{19}H_{22}O_3$ requires C, 76.48%; H, 7.43%. $[\alpha]_D$ = + 38.5° (c 1.98, $CHCl_3$). ^{1}H-n.m.r.: δ 2.38 [1H, broad s, -O*H*]; 3.17 [1H, centre of m, ArC*H*<]; 3.71-3.84 [2H, m, -CH_2OH]; 3.86 & 3.96 [2H, AB part of ABX system, -CH_2OBn, J_{AB}=10.9, J_{AX} & J_{BX}=7.3, 5.3]; 4.51 [2H, dt, -$OCH_2CH{=}CH_2$, J=5.3, 1.5]; 4.55 [2H, s, -CH_2OPh]; 5.28 [1H, dq, -$OCH_2CH{=}CHH$ *trans* to -CH_2-, J=10.5, 1.4]; 5.40 [1H, dq, -$OCH_2CH{=}CHH$ *cis* to -CH_2-, J=17.3, 1.6]; 6.05 [1H, ddt, -$OCH_2CH{=}CH_2$, J=17.3, 10.5, 5.3]; 6.76-6.82 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.17-7.24 [1H, m, *H* meta to -OAllyl]; 7.28-7.39 [5H, m, aromatics of Bn].

(*R*)-2-[3-(Allyloxy)phenyl]-3-[(benzyloxy)methoxy]propan-1-ol 29d. **(*S*)-3-Acetoxy-2-[3-(allyloxy)-phenyl]-3-[(benzyloxy)methoxy]propane. a)** A solution of monoacetate **28** (1.75 g, 6.99 mmol) in dry CH_2Cl_2 (20 ml), previously cooled in an ice-bath, was treated with Hünig's base (1.70 ml, 9.76 mmol) and BOM-Cl (1.16 ml, 8.34 mmol) and then allowed to react at r. t. for 22 hrs. A further addition of both reagents (as above) was needed to have complete reaction after additional 4.5 hrs. The mixture was partitioned between water and Et_2O and extracted with the same solvent. The solvent was removed under reduced pressure and the crude product used as such in the next reaction. **b)** This compound was prepared following the general procedure for hydrolysis of acetyl group reported above, starting from crude product of the previous described reaction. Chromatography PE : Et_2O 8:2 → 2:8 gave **29d** as a colourless oil (2.12 g, 93% from **28**. R_f 0.24 (PE : Et_2O 1:1). Anal. found C, 73.30%; H, 7.30%. $C_{20}H_{24}O_4$ requires C, 73.15%; H, 7.37%. $[\alpha]_D$ = + 17.4° (c 1.80, $CHCl_3$). ^{1}H-n.m.r.: δ 2.05 [1H, t, -O*H*, J=6.2]; 3.12 [1H, quintuplet, ArC*H*<, J=6.5]; 3.80-4.02 [4H, m, -CH_2OH + -CH_2OBOM]; 4.53 [2H, dt, -$OCH_2CH{=}CH_2$, J=5.3, 1.4]; 4.56 [2H, s, -OCH_2Ph]; 4.77 [2H, s, -OCH_2O-]; 5.29 [1H, dq, -$OCH_2CH{=}CHH$ *trans* to -CH_2-, J=10.3, 1.4]; 5.41 [1H, dq, -$OCH_2CH{=}CHH$ *cis* to -CH_2-, J=17.3, 1.6]; 6.06 [1H, ddt, -$OCH_2CH{=}CH_2$, J=17.3, 10.6, 5.4]; 6.76-6.82 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 6.79-6.86 [3H, m, aromatics]; 7.20-7.38 [6H, m, *H* meta to -OAllyl + aromatics of Bn]

(*S*)-2-[3-(Allyloxy)phenyl]-3-[(*t*-butyldiphenylsilyl)oxy]propanoic acid 30a. It was prepared from **29a** by the same procedure above described for the oxidation of **11** to **12**. Chromatography with PE : AcOEt 2:1, then 2:1 + 0.5% AcOH, then 1:1 + 0.5% AcOH, gave pure **30a** in 86% yield. R_f 0.55 (PE : AcOEt 1:1 + 0.5% AcOH). ^{1}H-n.m.r.: δ 1.01 [9H, s, *t*Bu-]; 3.79-3.87 [2H, m, -*CH*HOTBDPS + ArC*H*<]; 4.22 [1H, t, -CH*H*OTBDPS, J=11.0]; 4.46 [2H, dt, -$OCH_2CH{=}CH_2$, J=5.3, 1.5]; 5.25 [1H, dq, -$OCH_2CH{=}CHH$ *trans* to

-CH_2-, J=10.4, 1.4]; 5.37 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.2, 1.6]; 6.01 [1H, ddt, -OCH_2CH=CH_2, J=17.3, 10.6, 5.3]; 6.78-6.85 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.14-7.22 [1H, m, *H* meta to -OAllyl]; 7.25-7.39 [6H, m, *H* meta & para of -Si*Ph*$_2$*t*Bu]; 7.57-7.64 [4H, m, *H* ortho of -Si*Ph*$_2$*t*Bu].

(*S*)-2-[3-(Allyloxy)phenyl]-3-[(4-methoxybenzyl)oxy]propanoic acid 30b. It was prepared from **29a** by the same procedure above described for the oxidation of **11** to **12**. Chromatography with PE : AcOEt 6:4 → 1:1, then PE : AcOEt 1:1 + 0.5% AcOH gave pure **30b** in 87% yield. R_f 0.35 (PE : AcOEt 4:6. ^{1}H-n.m.r.: δ 3.65 [1H, X part of ABX system, ArC*H*<]; 3.80 [3H, s, -OCH_3]; 3.89 & 4.00 [2H, AB part of ABX system, -CH_2OMPM, J_{AB}=9.2, J_{AX} & J_{BX}=8.9, 5.0]; 4.48 & 4.52 [2H, AB system, -OCH_2[(4-OMe)Ph], J=12.0]; 4.50-4.52 [2H, m, -OCH_2CH=CH_2]; 5.27 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.5, 1.4]; 5.40 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.3, 1.6]; 6.04 [1H, ddt, -CH_2CH=CH_2, J=17.3, 10.5, 5.3]; 6.81-6.90 [5H, m, aromatics]; 7.20-7.26 [3H, m, aromatics].

(*S*)-2-[3-(Allyloxy)phenyl]-3-(benzyloxy)propanoic acid 30c. It was prepared from **29a** by the same procedure above described for the oxidation of **11** to **12**. Chromatography with PE : AcOEt 2:1, then 2:1 + 0.5% AcOH, then 6:4 + 0.5% AcOH gave pure **30c** in 91% yield. R_f 0.30 (PE : AcOEt 2:1 + 0.5% AcOH). $[\alpha]_D$ = + 42.6° (c 2.10, $CHCl_3$). ^{1}H-n.m.r.: δ 3.68 [1H, X part of ABX, ArC*H*<]; 3.91 & 4.03 [2H, AB part of ABX system, -CH_2OPh, J_{AB}=9.1, J_{AX} & J_{BX}=8.9, 4.4]; 4.50 [2H, dt, -OCH_2CH=CH_2, J=5.2, 1.5]; 4.53 & 4.58 [2H, AB system, -CH_2OPh, J=12.2]; 5.27 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.5, 1.5]; 5.39 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.3, 1.6]; 6.03 [1H, ddt, -CH_2CH=CH_2, J=17.3, 10.4, 5.2]; 6.81-6.91 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.23 [1H, t, *H* meta to -OAllyl, J=8.1]; 7.27-7.31 [5H, m, aromatics of Bn].

(*d,l*)-Ethyl 4-[3-(allyloxy)phenyl]-5-[(*t*-butyldiphenylsilyl)oxy]-3-oxopentanoate 31a. It was prepared from **30a** following the procedure already described in ref. 4. Chromatography with PE : Et_2O 8:2 gave pure **31a** (90%) as a colourless oil. This compound was found to be racemic, due to complete loss of stereochemical integrity during this reaction. R_f 0.30 (PE : Et_2O 8:2). Anal. found C, 72.60%; H, 7.15%. $C_{32}H_{38}O_5Si$ requires C, 72.42%; H, 7.22%. ^{1}H-n.m.r.: δ 1.00 [9H, s, *t*Bu-]; 1.21 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 3.42 & 3.49 [2H, AB system, -CH_2CO_2Et, J=15.5]; 3.81 [1H, X part of ABX system, ArC*H*<]; 4.07 & 4.23 [2H, AB part of ABX system, -CH_2OTBDPS, J_{AB} = 7.8, J_{AX} & J_{BX}=9.7, 5.9]; 4.12 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.46 [2H, dt, -OCH_2CH=CH_2, J=5.3, 1.5]; 5.27 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.5, 1.4]; 5.39 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.2, 1.6]; 6.03 [1H, ddt, -OCH_2CH=CH_2, J=17.3, 10.6, 5.3]; 6.71-6.85 [3H, m, 1*H* para & 2*H* ortho to -OAllyl]; 7.20 [1H, t, *H* meta to -OAllyl, J=7.9]; 7.34-7.45 [6H, m, *H* meta & para of -Si*Ph*$_2$*t*-Bu]; 7.60-7.65 [4H, m, *H* ortho of -Si*Ph*$_2$*t*-Bu].

(*d,l*)-Ethyl 4-[3-(allyloxy)phenyl]-5-[(4-methoxybenzyl)oxy]-3-oxopentanoate 31b. It was prepared from **30a** following the procedure already described in ref. 4. Chromatography with PE : Et_2O 8:2 gave pure **31b** (71%) as a colourless oil. This compound was found to be racemic, due to complete loss of stereochemical integrity during this reaction. R_f 0.39 (PE : Et_2O 6:4). Anal. found C, 69.75%; H, 6.90%. $C_{24}H_{28}O_6$ requires C, 69.89%; H, 6.84%. ^{1}H-n.m.r.: δ 1.20 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 3.40 & 3.46 [2H, AB system, -CH_2CO_2Et, J=15.5]; 3.61 [1H, X part of ABX system, ArC*H*<]; 3.80 [3H, s, -OCH_3]; 4.04 & 4.11 [2H, AB part of ABX system, -CH_2OMPM, J_{AB}=8.2, J_{AX} & J_{BX}=8.4, 6.1]; 4.10 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.39 & 4.46 [2H, AB system, -OCH_2[(4-OMe)Ph], J=11.7]; 4.50 [2H, dt, -OCH_2CH=CH_2, J=5.3, 1.5]; 5.29 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.3, 1.3]; 5.41 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.2, 1.6]; 6.04 [1H, ddt, -OCH_2CH=CH_2, J=17.2, 10.5, 5.3]; 6.76-6.88 [5H, m, aromatics]; 7.16-7.27 [3H, m, aromatics].

(*S*)-Ethyl 4-[3-(allyloxy)phenyl]-5-benzyloxy-3-oxopentanoate 31c. Preparation of imidazolide of **30c**: acid **30c** (1.00 g, 3.20 mmol) was dissolved in dry THF (10 ml) and stirred at r. t. for 5 min in the presence of powdered 4 Å molecular sieves (about 20 mg). The mixture was treated with 1,1'-carbonyldiimidazole (584 mg, 3.60 mmol) and stirred again for 10 min. Reaction: 48 ml of a 0.24 M solution of LDA (THF : hexanes about 8:2) were poured into a two necked flask equipped with two addition funnels; one of them was externally cooled to -78°C. After cooling the solution to -78°C, dry AcOEt (4.62 ml, 47.30 mmol) was added dropwise and the resulting solution was stirred for 10 min at the same temperature. After this time the imidazolide solution was added dropwise from the addition funnel into the flask, using additional 10 ml of THF to rinse the glassware. After 15 min an equivalent quantity of AcOEt enolate, prepared in a different flask, was dropped into the reaction using the cooled addition funnel. After 1 hr 40 min the reaction was quenched with NH_4Cl (sat. sol.) and the pH adjusted to 2 by careful addition of 1 N HCl. The two layer

system was saturated with NaCl and extracted with AcOEt. The combined organic layers ware washed with brine and dried over Na_2SO_4. After solvent removal under reduced pressure, chromatography with PE : Et_2O 85:15 → 7:3 gave pure **31c** (465 mg, 38%, 77% on unrecovered **30c**) as a colourless oil; by further elution with PE : AcOEt 1:1 in the presence of 2% AcOH also unreacted **30c** was recovered (507 mg, 51%). R_f 0.23 (PE : Et_2O 8:2). Anal. found C, 72.35%; H, 6.80%. $C_{23}H_{26}O_5$ requires C, 72.23%; H, 6.85%. $[\alpha]_D$ = - 92.7° (c 1.94, $CHCl_3$). ^{1}H-n.m.r.: δ 1.19 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 3.40 & 3.47 [2H, AB system, -CH_2CO_2Et. J=15.5]; 3.64 [1H, X part of ABX system, ArC*H*<]; 4.08 & 4.14 [2H, AB part of ABX system, -CH_2, J_{AB} = 8.3, J_{AX} & J_{BX}=8.4, 5.0]; 4.10 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.46 & 4.53 [2H, AB system, -CH_2Ph, J=12.4]: 4.47-4.51[2H, m, -OCH_2CH=CH_2]; 5.28 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.4, 1.4]; 5.40 [1H. dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.2, 1.5]; 6.03 [1H, ddt, -OCH_2CH=CH_2, J=17.3, 10.5, 5.2]; 6.78-6.87 [3H, m, *H* para & 2*H* ortho to -OAllyl]; 7.17-7.37 [6H, m, *H* meta to -OAllyl & aromatics of Bn].

(*S*)-Ethyl 5-benzyloxy-3,3-ethylendithio-4-[3-[(hydroxy)phenyl]pentanoate 17. a) (*S*)-Ethyl 5-benzyloxy-4-[3-(hydroxy)phenyl]-3-oxopentanoate 15. Compound **31c** (432 mg, 1.13 mmol) was dissolved in dry toluene (15 ml) and treated with $Pd(PPh_3)_4$ (131 mg, 113 μmol), AcOH (107 μl, 1.70 mmol) and *n*-Bu_3SnH (608 μl, 2.26 mmol). The resulting solution was heated at 80°C for 4 hrs. Tin derived by-products were mostly removed by the procedure reported by Bonini and Righi[42] during the extractive work-up, partitioning the mixture between CH_3CN and hexane. Chromatography (PE : Et_2O 1:1 → 4:6) gave **15** as a colourless oil (313 mg, 81%). **b**) The dithiolane protecting group was introduced as described for racemic **15**. $[\alpha]_D$ = - 9.2°(c 1.48, $CHCl_3$).

General procedure for Swern oxidation of 32. A solution of oxalyl chloride (868 μl of a 2.88 M solution in CH_2Cl_2, 2.5 mmol) was diluted with dry CH_2Cl_2 (2.5 ml), treated with 20 mg of powdered 4Å molecular sieves and cooled to -78°C, after 15 min stirring at r. t.. A solution of dimethyl sulfoxide (1.42 ml of a 2.82 M solution in CH_2Cl_2, 4.0 mmol) was added and the resulting solution was stirred for 10-12 min at -78°C. At this point a solution of **32**[28] (242 mg, 1.0 mmol) in CH_2Cl_2 (6 ml), previously stirred at r. t. for 30 min in the presence of 20 mg of powdered 4 Å sieves, was dropped into the reaction flask and stirring was continued at the same temperature for 10 min. Finally the desired amine (7.0 or 9.0 mmol) was added and the resulting mixture was stirred at the desired temperature for a suitable time as reported in Table 1. Work-up for reaction reported in entry 1 required dilution of crude mixture with water and extraction in alkaline medium with Et_2O. In all the other cases the mixture was diluted with 5% aqueous $NH_4H_2PO_4$ (10-15 ml) previously added with 7 ml of 1 N HCl, in order to perform the extraction from pH = 3. Usual extraction with Et_2O and solvent removal gave crude aldehyde **33**, which was reduced under standard conditions with $NaBH_4$ to give **32**, used to test racemization.

(*S*)-Methyl 2-[3-(allyloxy)phenyl]-2-[(benzyloxy)methoxy]-N-methyl-hydroxamate 34. Alcohol **29d** was oxidized to **30d** (R_f 0.35, PE : Et_2O 2:8) as above described for the oxidation of **11** to **12**. Crude **30d** (from 6.45 mmol of **29d**) was dissolved in THF (90 ml). A solution of N,O-dimethylhydroxylamine hydrochloride (1.30 g, 12.91 mmol) in water (30 ml) was added and the pH adjusted to 4.5 with 1 N NaOH. WSC [1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, 2.48 g, 12.91 mmol] dissolved in water (50 ml) was added from an addition funnel, over a period of 20 min. After 1.5 hrs stirring at r. t. the reaction was saturated with NaCl and extracted with AcOEt. After solvent removal, chromatography with PE : Et_2O 6:4 → 3:7 gave pure **34** as a colourless oil (1.69 g, 73% from **29d**). R_f 0.23 (PE : Et_2O 8:2). Anal. found C, 68.70%; H, 7.00%, N, 3.70%. $C_{22}H_{27}NO_5$ requires C, 68.55%; H, 7.06%, N, 3.63%. $[\alpha]_D$ = - 40.3° (c 1.86, $CHCl_3$). IR: ν_{max} 2996, 2882, 1658, 1599, 1585, 1448, 1192, 993. ^{1}H-n.m.r.: δ 3.19 [3H, s, >NCH_3]; 3.51 [3H, s, -OCH_3]; 3.75 [1H, dd, >C*H*CH_2OBOM, J=8.8, 4.8]; 4.22 [1H, t, -C*H*HOBOM, J=9.1]; 4.22-4.38 [1H, m, -CH*H*OBOM]; 4.51 [2H, dt, -OCH_2CH=CH_2, J=5.4, 1.5]; 4.52 & 4.55 [2H, AB system, -CH_2Ph, J=11.7]; 4.74 & 4.77 [2H, AB system, -OCH_2O-, J=6.7]; 5.28 [1H, dq, -OCH_2CH=C*H*H *trans* to -CH_2-, J=10.4, 1.4]; 5.41 [1H, dq, -OCH_2CH=C*H*H *cis* to -CH_2-, J=17.3, 1.6]; 6.04 [1H, ddt, -OCH_2CH=CH2, J=17.2, 10.5, 5.2]; 6.81 [1H, ddd, *H* ortho to -OAllyl & para to the side chain]; 6.91-6.94 [2H, m, *H* ortho to both substituents & *H* para to -OAllyl]; 7.22 [1H, t, *H* meta to OAllyl, J=8.2]; 7.30-7.37 [5H, m, aromatics of -BOM].

(*S*)-2-[3-(allyloxy)phenyl]-1-[(benzyloxy)methoxy]pentan-3-one 35. A solution of **34** (1.21 g, 3.14 mmol) in dry THF was cooled to -78°C and treated with EtMgBr (3.38 ml of a 3 M solution in Et_2O, 10.14 mmol).

The temperature was then allowed to rise to 0°C and the solution was stirred at this temperature for 6 hrs. After quenching with saturated aqueous NH_4Cl, the reaction was extracted with Et_2O. After solvent removal under reduced pressure, chromatography with PE : Et_2O 95:5 → 3:7 gave **35** as a colourless oil (988 mg, 89%). R_f 0.45 (PE : Et_2O 8:2). Anal. found C, 74.35%; H, 7.35%. $C_{22}H_{26}O_4$ requires C, 74.55%; H, 7.39%. $[\alpha]_D$ = - 131.7° (c 2.04, $CHCl_3$). IR: ν_{max} 2937, 2881, 1713, 1599, 1584, 1448, 1195, 1112, 1021. ^{1}H-n.m.r.: δ 0.99 [3H, t, -CH_2CH_3, J=7.3]; 2.46 [2H, centre of m, -CH_2CH_3]; 3.72 [1H, dd, >$CH$$CH_2$OBOM, J=9.3, 5.4]; 3.95 [1H, dd, -CHHOBOM, J=8.7, 5.4]; 4.23 [1H, t, -CHHOBOM, J=9.0]; 4.38-4.57 [4H, m, -OCH_2CH=CH_2 & -CH_2Ph]; 4.70 & 4.74 [2H, AB system, -OCH_2O-, J=6.8]; 5.28 [1H, dq, -OCH_2CH=CHH *trans* to -CH_2-, J=10.4, 1.4]; 5.30 [2H, s, -OCH_2O-]; 5.41 [1H, dq, -OCH_2CH=CHH *cis* to -CH_2-, J=17.3, 1.6]; 6.04 [1H, ddt, -OCH_2CH=CH_2, J=17.0, 10.5, 5.3]; 6.79-6.85 [3H, m, 2H ortho to -OAllyl & H ortho to the side chain]; 7.23 [1H, t, H meta to both substituents, J=7.2]; 7.30-7.36 [5H, m, aromatics of -BOM].

(3*R*,4*S*)-Ethyl 4-[3-(allyloxy)phenyl]-5-[(benzyloxy)methoxy]-3-ethyl-3-hydroxypentanoate 36b. A 0.25 M solution of LDA (6.9 ml in THF : hexanes about 8:2) was cooled to -78°C and treated with AcOEt (172 µl, 1.76 mmol). After 10 min ketone **35**, (208 mg, 587 µmol), dissolved in dry THF (5 ml) was added dropwise to the enolate solution and the resulting mixture was stirred at -78°C for 1 hr, until complete. Quenching with saturated aqueous NH_4Cl and extraction with Et_2O followed by chromatography with PE : Et_2O 9:1 → 1:1 gave **36b**, containing ≈ 10% of the C_3 epimer as well as some AcOEt derived by-products. This crude compound was not further purified, but it was used as such for the next reaction. R_f 0.41 (PE : Et_2O 6:4). IR: ν_{max} 2967, 2935, 2432, 1710, 1373, 1189, 1021. ^{1}H-n.m.r. (major isomer): δ 0.87 [3H, t, -CH_2CH_3, J=7.4]; 1.28 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 1.51 [2H, centre of m, -CH_2CH_3]; 2.56 [2H, s, -CH_2CO_2Et]; 3.16 [1H, X part of ABX system, >$CH$$CH_2$OBOM]; 3.86 [1H, s, -O$H$]; 4.02 & 4.15 [2H, AB part of ABX system, -CH_2OBOM, J_{AB}=10.0, J_{AX} & J_{BX}=7.7, 4.0]; 4.17 [2H, q, -OCH_2CH_3, J=7.3]; 4.44 [2H, s, -CH_2Ph]; 4.50 [2H, dt, -OCH_2CH=CH_2, J=5.3, 1.4]; 4.68 & 4.72 [2H, AB system, -OCH_2O-, J=6.8]; 5.27 [1H, dq, -OCH_2CH=CHH *trans* to -CH_2-, J=10.5, 1.4]; 5.40 [1H, dq, -OCH_2CH=CHH *cis* to -CH_2-, J=17.3, 1.6]; 6.05 [1H, ddt, -OCH_2CH=CH_2, J=17.3, 10.6, 5.4]; 6.77-6.96 [3H, m, 2H ortho to -OAllyl & H ortho to the side chain]; 7.20 [1H, t, H meta to both substituents, J=7.9]; 7.28-7.37 [5H, m, aromatics of -BOM].

(3*R*,4*S*)-Ethyl 5-[(benzyloxy)methoxy]-3-ethyl-4-(3-hydroxyphenyl)-3-(triethylsilyloxy)pentanoate 37. a) (3*R*,4*S*)-Ethyl 4-[3-(allyloxy)phenyl]-5-[(benzyloxy)methoxy]-3-ethyl-3-(triethylsilyloxy)pentanoate. A solution of **36b** (265 mg, < 587 µmol) in dry CH_2Cl_2 (2 ml) was cooled to 0°C and treated with 2,6-lutidine (308 µl, 2.64 mmol) and trietylsilyltriflate (398 µl, 1.76 mmol). After stirring at the same temperature for 30 min the reaction was diluted with Et_2O and pH adjusted to 1 by slow addition of 1 M HCl; the reaction was rapidly extracted with Et_2O and the combined organic layers, after washing until neutral with $NaHCO_3$ and brine, were concentrated under reduced pressure. Chromatography with PE : Et_2O 95:5 → 8:2 gave a pure 9:1 mixture of the 3*R* alcohol and its 3*S* epimer as a colourless oil (262 mg, 80% from **35**). R_f 0.24 (PE : Et_2O 9:1). $[\alpha]_D$ = - 1.84° (c 1.90, $CHCl_3$). IR: ν_{max} 2951, 2875, 1727, 1453, 1162, 1111, 1019. ^{1}H-n.m.r. (major isomer): δ 0.62 [6H, centre of m, -Si(CH_2CH_3)$_3$]; 0.82 [3H, t, -CH_2CH_3, J=7.4]; 0.93 [9H, t, -Si(CH_2CH_3)$_3$, J=7.7]; 1.26 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 1.43-1.69 [2H, m, -CH_2CH_3]; 2.62 & 2.81 [2H, AB system, -CH_2CO_2Et, J=15.0]; 3.35 [1H, X part of ABX system, >$CH$$CH_2$OBOM]; 3.95 & 4.15 [2H, AB part of ABX system, -CH_2OBOM, J_{AB}=9.7, J_{AX} & J_{BX}=8.6, 5.1]; 4.10 [2H, q, -OCH_2CH_3, J=7.1]; 4.36 & 4.40 [2H, AB system, -CH_2Ph, J=11.8]; 4.49 [2H, dt, -OCH_2CH=CH_2, J=5.2, 1.5]; 4.63 & 4.69 [2H, AB system, -OCH_2O-, J=6.7]; 5.26 [1H, dq, -OCH_2CH=CHH *trans* to -CH_2-, J=10.5, 1.8]; 5.39 [1H, dq, -OCH_2CH=CHH *cis* to -CH_2-, J=17.2, 1.6]; 6.05 [1H, ddt, -OCH_2CH=CH_2, J=17.5, 10.5, 5.4]; 6.75-6.94 [3H, m, 2H ortho to -OAllyl & H ortho to the side chain]; 7.17 [1H, t, H meta to both substituents, J=8.1]; 7.25-7.32 [5H, m, aromatics of -BOM]. **b)** The same procedure reported for transformation of **31c** into **15** was followed. Chromatography with PE : Et_2O 8:2 → 3:7 gave a pure 9:1 mixture of **37** and its C_3 epimer as a colourless oil (200 mg, 82%) R_f 0.24 (PE : Et_2O 9:1). $[\alpha]_D$ = - 0.69° (c 2.62, $CHCl_3$). IR: ν_{max} 3008, 1726, 1445, 1391, 1185, 1029. ^{1}H-n.m.r. (major isomer): δ 0.62 [6H, centre of m, -Si(CH_2CH_3)$_3$]; 0.83 [3H, t, -CH_2CH_3, J=7.4]; 0.93 [9H, t, -Si(CH_2CH_3)$_3$, J=7.8]; 1.26 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 1.38-1.69 [2H, m, -CH_2CH_3]; 2.62 & 2.79 [2H, AB system, -CH_2CO_2Et, J=15.0]; 3.32 [1H, X part of ABX system, >$CH$$CH_2$OBOM]; 3.95 & 4.14 [2H, AB part of ABX system, -CH_2OBOM, J_{AB}=9.7, J_{AX} & J_{BX}=8.8, 4.7]; 4.10 [2H, q, -OCH_2CH_3, J=7.2]; 4.37 & 4.41 [2H, AB system, -CH_2Ph, J=12.0]; 4.63 & 4.69 [2H, AB system, -OCH_2O-, J=5.8]; 6.69

[1H, ddd, *H* ortho to -OH & para to substituent, J=8.0, 5.1, 0.9]; 6.81 [1H, broad t, *H* ortho to both substituents, J=1.9]; 6.90 [1H, broad d, *H* ortho to the side chain & para to -OH, J=7.8]; 7.13 [1H, t, *H* meta to both substituents, J=7.8]; 7.27-7.33 [5H, m, aromatics of -BOM]. ^{13}C-n.m.r. (major isomer): δ 6.97 [3C, -Si(*C*H$_2$CH$_3$)$_3$]; 7.22 [3C, -Si(CH$_2$*C*H$_3$)$_3$]; 8.54 [>C(OTES)CH$_2$*C*H$_3$]; 14.14 [-OCH$_2$*C*H$_3$]; 32.26 [>C(OTES)*C*H$_2$CH$_3$]; 43.11 [-*C*H$_2$CO$_2$Et]; 52.97 [Ar*C*H<]; 60.33 [-O*C*H$_2$CH$_3$]; 68.89 & 69.09 [2C, -*C*H$_2$OBOM & -OCH$_2$Ph]; 78.95 [>*C*(OTES)CH$_2$CH$_3$]; 94.44 [-OCH$_2$O-]; 113.54 [*C* ortho to both substituents]; 117.21 [*C* ortho to -OH & para to the side chain]; 122.56 [*C* para to -OH & ortho to the side chain]; 127.52 [Ar*C* para of -Ph]; 127.82 & 128.30 [4C, Ar*C* ortho & meta of -Ph]; 128.74 [*C* meta to both substituents]; 137.99 [Ar*C* ipso of -Ph]; 142.22 [quaternary *C* meta to -OH]; 155.16 [aromatic *C*-OH]; 170.63 [>*C*=O].

(1*R*,3*R*,4*S*)- and (1*S*,3*R*,4*S*)-4-[(benzyloxy)methoxy]methyl-3-ethyl-3-(triethylsilyloxy)-1,2,3,4-tetrahydronaphthalene-1,8-diols 38a,b. The procedure reported in ref. 4 was followed starting from 907 mg of **37** (1.76 mmol). Compounds **38a** and **38b** were obtained. During this cyclization some diol, derived from the complete reduction of the ester function was also obtained together with some unreacted **37**. Due to the difficulty to separate **37** from **38b**, we preferred to treat the crude cyclization mixture with DIBALH (8.78 ml of a 1 M solution in CH_2Cl_2, 8.78 mmol), in order to reduce the unreacted ester. The reaction was performed between -78°C and 0°C, and the work-up was the same as in the cyclization reaction. Chromatography with PE : Et_2O 6:4 → Et_2O gave **38a,b** as a colourless oil (615 mg, 74%) in a 41 : 59 diastereomeric ratio, accompanied by small amounts of the C_3 epimers. Also 179 mg of diol (22%) were obtained. The two diastereomers **38a,b** were separated by preparative thin layer chromatography, using PE : Et_2O 6:4 as eluent. Small amounts of the C_3 epimers were still visible at ^{1}H-n.m.r.. Characterization of **38a**: R_f 0.44 (PE : Et_2O 6:4). $[\alpha]_D$ = - 11.5° (c 1.29, $CHCl_3$). IR (mixture **38a,b**): ν_{max} 3437, 3386, 3003, 2954, 1589, 1459, 1108. ^{1}H-n.m.r.: δ 0.42 [6H, centre of m, -Si(C*H*$_2$CH$_3$)$_3$]; 0.74 [9H, t, -Si(CH$_2$C*H*$_3$)$_3$, J=7.8]; 1.05 [3H, t, -CH$_2$C*H*$_3$, J=7.4]; 1.71 [2H, q, -C*H*$_2$CH$_3$, J=7.4]; 2.12 [1H, dd, H_2, J=14.7, 6.1]; 2.30 [1H, dt, $H_{2'}$, J=12.8, 1.9]; 2.95 [1H, centre of m, H_4]; 3.38 [1H, d, R-O*H*, J=11.2]; 3.71 & 3.82 [2H, AB part of ABX system, -C*H*$_2$OBOM, J_{AB}=10.2, J_{AX} & J_{BX}=4.7, 4.5]; 4.36 [2H, s, -C*H*$_2$Ph]; 4.60 & 4.63 [2H, AB system, -OC*H*$_2$O-, J=6.8]; 4.86 [1H, ddd, H_1, J=11.1, 5.9, 1.8]; 6.82 [2H, 2 overlapped d, H_5 + H_7, J=8.2]; 7.08 [1H, s, Ar-O*H*]; 7.17 [1H, t, H_6, J=7.8]; 7.19-7.38 [5H, m, aromatics of -BOM]. ^{13}C-n.m.r.: δ 6.53 [3C, -Si(*C*H$_2$CH$_3$)$_3$]; 6.87 [3C, -Si(CH$_2$*C*H$_3$)$_3$]; 7.59 [>C(OTES)CH$_2$*C*H$_3$]; 30.78 [>C(OTES)*C*H$_2$CH$_3$]; 37.94 [C_2]; 51.21 [C_4]; 65.23 [C_1]; 69.51 & 70.28 [2C, -*C*H$_2$OBOM & -O*C*H$_2$Ph]; 77.73 [C_3]; 94.58 [-OCH$_2$O-]; 114.62 [C_7]; 121.57 [C_5]; 124.66 [C_{8a}]; 127.52 [Ar*C* para of -Ph]; 127.81 & 128.56 [4C, Ar*C* ortho & meta of -Ph]; 128.76 [C_6]; 136.95 & 137.63 [2C, Ar*C* ipso of -Ph & C_{4a}]; 156.08 [C_8]. Characterization of **38b**: R_f 0.36 (PE : Et_2O 6:4). $[\alpha]_D$ = - 31.3° (c 1.96, $CHCl_3$). ^{1}H-n.m.r.: δ 0.40 [6H, centre of m, -Si(C*H*$_2$CH$_3$)$_3$]; 0.74 [9H, t, -Si(CH$_2$C*H*$_3$)$_3$, J=7.8]; 1.01 [3H, t, -CH$_2$C*H*$_3$, J=7.4]; 1.59-1.73 [2H, m, -C*H*$_2$CH$_3$]; 1.82 [1H, dd, H_2, J=12.8, 9.6]; 2.12 [1H, broad d, R-O*H*, J=7.1]; 2.42 [1H, ddd, $H_{2'}$, J=12.8, 7.0, 1.9]; 2.85 [1H, centre of m, H_4]; 3.75 & 3.78 [2H, AB part of ABX system, -C*H*$_2$OBOM, J_{AB}=10.1, J_{AX} & J_{BX}=4.5, 4.3]; 4.29 [2H, s, -C*H*$_2$Ph]; 4.57 & 4.59 [2H, AB system, -OC*H*$_2$O-, J=6.9]; 5.14 [1H, broad dt, H_1, J=9.1, ≈ 8]; 6.75 [2H, 2 overlapped d, H_5 + H_7, J=8.0]; 7.13 [1H, t, H_6, J=8.0]; 7.19-7.38 [5H, m, aromatics of -BOM]; 8.16 [1H, s, Ar-O*H*]. ^{13}C-n.m.r.: δ 6.58 [3C, -Si(*C*H$_2$CH$_3$)$_3$]; 6.91 [3C, -Si(CH$_2$*C*H$_3$)$_3$]; 7.34 [>C(OTES)CH$_2$*C*H$_3$]; 32.30 [>C(OTES)*C*H$_2$CH$_3$]; 40.67 [C_2]; 50.38 [C_4]; 68.42 [C_1]; 69.33 & 70.71 [2C, -*C*H$_2$OBOM & -OCH$_2$Ph]; 77.49 [C_3]; 94.41 [-O*C*H$_2$O-]; 114.24 [C_7]; 121.54 [C_5]; 123.49 [C_{8a}]; 127.73 [Ar*C* para of -Ph]; 127.90 & 128.40 [4C, Ar*C* ortho & meta of -Ph]; 128.95 [C_6]; 137.56 & 138.55 [2C, Ar*C* ipso of -Ph & C_{4a}]; 156.38 [C_8]. The configuration at C_1 for **38a,b** was not determined.

(1*R*,3*R*,4*S*)- and (1*S*,3*R*,4*S*)-4-[(benzyloxy)methoxy]methyl-3-ethyl-1-hydroxy-8-methoxy-3-(triethylsilyloxy)-1,2,3,4-tetrahydronaphthalene 39a,b. A solution of **38a,b** (136 mg, 288 μmol) in dry acetone (6 ml) was treated with anhydrous K_2CO_3 (199 mg, 1.44 mmol), CH_3I (179 μl, 2.88 mmol) and then refluxed for 2.5 hrs. Solid K_2CO_3 was filtered off and solvent removed under reduced pressure. Chromatography with PE : Et_2O 8:2 → 1:1 gave **39a,b** as a colourless oil (133 mg, 96%). Since **39a,b** turned out to be difficult to separate, for analytical purposes, they were separately synthesized from **38a** and **38b**. Characterization of **39a** (this diastereomer is the faster running in t.l.c., but is derived from diol **38b**, the slower running one): R_f 0.57 (PE : Et_2O 1:1). ^{1}H-n.m.r.: δ 0.42 [6H, centre of m, -Si(C*H*$_2$CH$_3$)$_3$]; 0.75 [9H, t, -Si(CH$_2$C*H*$_3$)$_3$, J=7.8]; 1.00

[3H, t, -CH_2CH_3, J=7.3]; 1.48-1.76 [2H, m, -CH_2CH_3]; 1.85 [1H, dd, H_2, J=13.7, 8.0]; 2.35 [1H, ddd, H_2, J=13.6, 7.6, 1.8]; 2.93 [1H, centre of m, H_4]; 3.72 & 3.90 [2H, AB part of ABX system, -CH_2OBOM, J_{AB}=9.9, J_{AX} & J_{BX}=6.1, 4.4]; 3.88 [3H, s, -OCH_3]; 4.44 [2H, s, -CH_2Ph]; 4.67 [2H, s, -OCH_2O-]; 5.13 [1H, dt, H_1, J=7.8, 7.7]; 6.75 [1H, d, H_7, J=8.1]; 6.91 [1H, d, H_5, J=7.7]; 7.19 [1H, t, H_6, J=7.9]; 7.23-7.38 [5H, m, aromatics of -BOM]. Characterization of **39b** (this diastereomer is the slower running in t.l.c., but is derived from diol **38a**, the faster running one): R_f 0.48 (PE : Et_2O 1:1). ^{1}H-n.m.r.: δ 0.58 [6H, centre of m, -$Si(CH_2CH_3)_3$]; 0.75 [9H, t, -$Si(CH_2CH_3)_3$, J=7.8]; 1.02 [3H, t, -CH_2CH_3, J=7.3]; 1.38-1.60 [2H, m, -CH_2CH_3]; 1.66 [1H, dd, H_2, J=7.5, 4.0]; 2.16-2.23 [2H, m, H_2]; 3.06 [1H, centre of m, H_4]; 3.73 & 3.92 [2H, AB part of ABX system, -CH_2OBOM, J_{AB}=10.2, J_{AX} & J_{BX}=9.0, 4.0]; 3.88 [3H, s, -OCH_3]; 4.42 [2H, s, -CH_2Ph]; 4.64 & 4.68 [2H, AB system, -OCH_2O-, J=6.7]; 5.00 [1H, dt, H_1, J=7.7, 5.2]; 6.77 [1H, d, H_7, J=8.1]; 6.96 [1H, d, H_5, J=8.8]; 7.22 [1H, t, H_6, J=8.0]; 7.24-7.37 [5H, m, aromatics of -BOM].

(3*R*,4*S*)-4-[(Benzyloxy)methoxy]methyl-3-ethyl-8-methoxy-3-(triethylsilyloxy)-1,2,3,4-tetrahydronaphthalene 40. A solution of **39a,b** (111 mg, 228 μmol) in dry CH_2Cl_2 (5 ml) was cooled to -78°C. Et_3SiH (55 μl, 342 μmol) and $EtAlCl_2$ (139 μl of a 1.8 M solution in toluene, 251 μmol) were added and the solution was stirred at the same temperature for 1 hr. The reaction was quenched with NH_4Cl (sat. aqueous solution), diluted with Et_2O and saturated Rochelle's salt aqueous solution and stirred until two clear layers were obtained. After extraction with Et_2O and solvent removal under reduced pressure a colourless oil was obtained, which was used as such in the next reaction. R_f 0.80 (PE : Et_2O 6:4).

(3*R*,4*S*)-4-[(Benzyloxy)methoxy]methyl-3-ethyl-3-hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene 41. The crude product just obtained as above described was dissolved in CH_3CN (4 ml) and cooled to 0°C. 40% HF (about 200 μl) was added and the solution was stirred at the same temperature for 2 hrs; then about 100 μl of HF were added again and stirring continued for an additional hr. The reaction was neutralized with $NaHCO_3$ and extracted with Et_2O. Solvent was removed and chromatography with PE : Et_2O 8:2 → 3:7 furnished pure **41** as a colourless oil (25.2 mg, 31% from **39a,b**). R_f 0.63 (PE : Et_2O 2:8). ^{1}H-n.m.r.: δ 1.03 [3H, t, -CH_2CH_3, J=7.4]; 1.50-1.65 [2H, m, -CH_2CH_3]; 1.69-1.84 & 1.88-2.03 [2H, 2 m, H_2]; 2.33 [1H, s, -O*H*]; 2.67 & 2.80 [2H, AB part of ABX system, H_1, J_{AB}=18.3, J_{AX} & J_{BX}=7.7, 6.1]; 3.19 [1H, t, H_4, J=6.2]; 3.82 [3H, s, -OCH_3]; 3.84 & 3.91 [2H, AB part of ABX system, -CH_2OBOM, J_{AB}=9.8, J_{AX} & J_{BX}=6.6, 5.9]; 4.47 [2H, s, -CH_2Ph]; 4.71 [2H, s, -OCH_2O-]; 6.70 [1H, d, H_7, J=8.1]; 6.85 [1H, d, H_5, J=7.7]; 7.13 [1H, t, H_6, J=8.0]; 7.27-7.38 [5H, m, aromatics of -BOM].

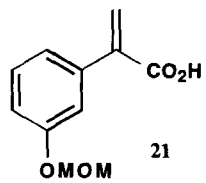
(3*R*,4*S*)-3-ethyl-3-hydroxy-4-(hydroxy)methyl-8-methoxy-1,2,3,4-tetrahydronaphthalene 42. A solution of **41** (23.8 mg, 66.8 μmol) in 96% EtOH (10 ml) was treated with 10% Pd over charcoal and hydrogenated at r. t. for 3 hrs. The catalyst was filtered off and the remaining solution concentrated *in vacuo* to give 13.4 mg of product (85%), pure at n.m.r. and t.l.c.. R_f 0.37 (PE : Et_2O 4:6). $[\alpha]_D$ = - 7.7° (c 0.67, $CHCl_3$). IR: ν_{max} 3595, 2934, 1585, 1463, 1103. ^{1}H-n.m.r.: δ 1.05 [3H, t, -CH_2CH_3, J=7.4]; 1.50-2.02 [4H, m, H_2 + -CH_2CH_3] 2.75 [2H, broad t, H_1, J=7.1]; 2.99 [1H, broad t, H_4, J≈5.4]; 3.83 [3H, s, -OCH_3]; 3.80 & 3.90 [2H, m, -CH_2OH]; 6.75 [1H, d, H_7, J=8.1]; 6.82 [1H, d, H_5, J=7.7]; 7.17 [1H, t, H_6, J=7.9]. ^{13}C-n.m.r.: δ 6.86 [>C(OH)CH_2CH_3]; 20.36 [-OCH_2CH_3]; 29.66 [C_2]; 31.01 [C_1]; 50.18 [C_4]; 55.26 [-OCH_3]; 64.56 [-CH_2OH]; 72.46 [C_3]; 107.9 [C_7]; 121.18 [C_5]; 125.23 [C_{8a}]; 126.70 [C_6]; 136.40 [C_{4a}]; 157.35 [C_8].

REFERENCES AND NOTES

1. Part of this work was reported in preliminary communications [**a**) Guanti, G.; Banfi, L.; Brusco, S.; Riva, R. *Tetrahedron Lett.* **1993**, *34*, 8549-8552; **b**) Guanti, G.; Riva, R. *Tetrahedron Lett.* **1995**, *36*, 3933-3936].
2. For some excellent reviews in the field of anthracyclinones see: **a**) Krohn, K. *Angew. Chem., Int. Ed. Engl.*, **1986**, *25*, 790-807; **b**) Krohn, K. *Tetrahedron* **1990**, *46*, 291-318; **c**) Thomas, J. I. 'Synthesis of Anthracyclines related to Daunomycin', in *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukas, G.; Ohno, M. Eds., Springer, Berlin, **1990**, p. 467-496.
3. Syntheses of **1**: **a**) McNamara, J. M.; Kishi, Y. *Tetrahedron* **1984**, *40*, 4685-4691; **b**) Rizzi, J. P.; Kende,

A. S. *Tetrahedron* **1984**, *40*, 4693-4700; syntheses of AB ring fragment **2**: **c**) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592-4597; **d**) Davis, F. A.; Kumar, A. *Tetrahedron Lett.* **1991**, *32*, 7671-7674.

4. Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1994**, *50*, 11945-11966.
5. Kitahara, T.; Touhara, K.; Watanabe, H.; Mori, K. *Tetrahedron* **1989**, *45*, 6387-6400.
6. Commercially available BOM-Cl was found to contain variable amounts of benzyl chloride. Thus, prior to use, it must be carefully purified by distillation over anhydrous $CaCl_2$; reagent must then be stored over $CaCl_2$ to ensure its stability over a long period of time; alternatively the best way is to freshly prepare this reagent (ref. Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckmann R. K.; Medwid J. B. *Org.* Synth., coll. vol. VI, 101-103).
7. We tried to optimize our purification procedure by using K_2CO_3 as drying agent for the organic extracts and by adding small amount of bases like Et_3N or Et_2NH either to the organic extract or to the eluent for chromatography on silica; but we never obtained pure **14** in acceptable yield and purity, although, as we found out lather, this compound is perfectly stable on silica, also without use of additives.
8. As we verified later on similar intermediates, compounds like **9** are activated to elimination processes under basic conditions: we frequently obtained elimination products like **21** (also in this case it was detected, even in small quantities, in the reaction mixture); probably, the presence of methanol gave in this case a Michael-type reaction, responsible for the formation of **10.**



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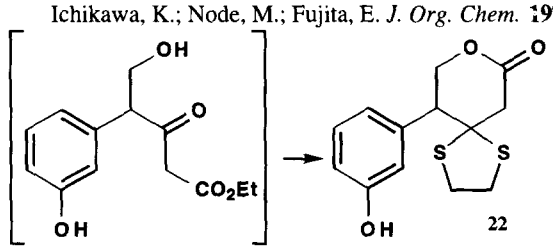
9. The reduction of the ester was never complete, also using an excess of DIBALH and was always accompanied by a small amount of the corresponding aldehyde: however the mixture can be oxidized as such to give **12**.
10. The direct homologation of ester **9** *via* Claisen-type reaction (ref. **a**) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318-2320; **b**) Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177-5180; **c**) Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753-2756) gave only a low conversion to desired **14** (24%).
11. **a**) Bram, G.; Vilkas, M. *Bull. Chem. Soc. Fr.* **1964**, 945-951; **b**) Shih, D. H., Baker, F., Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29-40.
12. A debenzylation method using boron trifluoride in the presence of a thiol is known (rif. Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661-1664).



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13. The resulting hydroxy ester rapidly cyclizes to give the six membered lactone **22** as soon as the carbonyl group is protected, but we never were able to utilize this lactone as intermediate for our synthetic purposes.
14. Use of purified 1,2-*bis*[(trimethylsilyl)thio]ethane (rif. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009-5017) under catalysis of various Lewis acids gave no protected **18**.
15. Also here, as reported in ref. 4, 1,8-dihydroxytetralins **19** and **21** were best characterized as the corresponding diacetates **20** e **22**.
16. **a**) Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron Lett.* **1990**, *46*, 7081-7092; **b**) Guanti, G.; Banfi, L.; Narisano E. *J. Org. Chem.* **1992**, *57*, 1540-1554.
17. **a**) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymmetry* **1994**, *5*, 9-12; **b**) Banfi, L.; Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 1345-1356.
18. Although MOM protecting group showed to be good for the planned synthesis, we did not use it due to the low e.e. of monoacetate (50%) obtained in monohydrolysis of the corresponding diacetate. [1a]
19. Diol **24** was prepared according to ref. 17b.
20. Anyway, in view of a total synthesis of **1**, a low stereoselectivity in the cyclization reaction is not a real problem; actually, it is known from the literature[3a] that the correct stereochemistry of carbon 7 of **1** (1 in compound **19**) can be established as the last step of the synthetic transformations by the

stereospecific introduction of the hydroxy group in the α position respect to ring.
21. The e.e. of monoprotected diols **29a-d** was verified by ^{1}H-n.m.r. analysis of the corresponding Mosher's esters (ref. Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147).
22. **a**) Standard conditions (ethanedithiol, $BF_3{\cdot}Et_2O$) gave deblocking of TBDPS group (27%) and lactonization to the analogous of **22** (54%). **b**) Conditions used successfully on **14** gave the same result. **c**) Conditions described in note 14 failed also in this case. Moreover, our attempts to open the lactone restoring the ester function failed.
23. **a**) Attempts to convert the carbonyl of **31a** into the corresponding dioxolane by treatment with ethylene glycol in the presence of camphorsulfonic acid gave partial hydrolysis of the ester function (39%) together with transesterification product (38%), due to the action of ethylene glycol; **b**) Use of 2-methoxy-1,3-dioxolane gave, instead of transketalization product, only the analogous of **31a** as methyl ester (22%).
24. **a**) Classical benzylation, that is treatment of the alcohol with NaH, followed by addition of benzyl bromide, furnished **29c** in low yield and extended racemization at the chiral centre. **b**) Use of benzyl bromide in the presence of Ag_2O (ref. 1) Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3940-3942; 2) Gargiulo, D.; Blizzard, T. A.; Nakanishi, K. *Tetrahedron* **1989**, *45*, 5423-5432) gave **29c** in good yield (81%) but with about 30% racemization. **c**) Benzylation with benzyl trichloroacetimidate catalyzed by trifluoromethanesulfonic acid (ref. Nakajiama, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139-4142) proved to be non-racemizing, but yield of **29c** was not reproducible and product, obtained by this procedure, was very difficult to purify.
25. MPM showed to be very ephemeral: a) procedure reported for compound **14**, gave deprotected ester (28%) together with the analogous of **22** (31%); b) the mild procedure reported in note 14 gave just deblocking of MPM group; c) attempts to protect ketone function after allyl removal also failed.
26. Due to the intrinsic enantiodivergency of compounds like **28** or ***ent*-28**, **29c** can also be prepared from **28** but through a two step longer sequence involving a supplementary protecting group (see ref. 1a).
27. The racemization was proved by ^{1}H-n.m.r. of β-ketoester **31c** in the presence of Eu(hfc)$_3$; since we were sure that the transformation of ***ent*-28** into acid **30a** was not-racemizing (as proved on very similar compounds)[28], the racemization has necessarily occurred at the homologation step.
28. Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1995**, *51*, 10343-10360.
29. See also ref. 1a.
30. Racemization was verified after reduction of **31c** with $NaBH_4$ to give a 77 : 23 diastereomeric mixture of the secondary alcohols (76% overall yield). The most abundant alcohol was then transformed into the corresponding Mosher's esters, then analyzed by ^{1}H-n.m.r.
31. The preparation of **32** in 97% enantiomeric excess was already described in ref. 28.
32. Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570-1576.
33. **a**) Banfi, L.; Guanti, G.; Narisano, E. *Tetrahedron* **1993**, *49*, 7385-7392; **b**) Guanti, G.; Banfi, L.; Riva, R.; Zannetti, M. T. *Tetrahedron Lett.* **1993**, *34*, 5483-5486.
34. A previous example of use of Hünig's base in a Swern oxidation has also been reported (ref. Walba, D. M.; Thurmes, W. N.; Altiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046-1056).
35. It was demonstrated by ^{1}H-n.m.r. analysis of the Mosher's esters of alcohol **32**, obtained *via* $NaBH_4$ reduction of **33**.
36. A side reaction responsible for the observed low yield is the chlorination at the benzylic position of **32**.
37. BOM group, which was directly introduced on **28** without racemization, was in this case the protection of choice since, for the planned synthesis, we did not foresee a thioketalization step, a transformation not consistent with an acetalic-like protection.
38. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
39. Diastereomeric ratio was in both cases around 9:1 and was determined by ^{1}H-n.m.r. analysis; the two diastereomers were not separated neither at the level of **36** nor in one of the following.
40. Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548-2560.
41. Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans 1* **1985**, 2247-2250.
42. Bonini, C.; Righi, G. *Tetrahedron* **1992**, *48*, 1531-1538.

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