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Regioselective Synthesis of 1,8-Dihydroxytetralins through a Tandem Reduction/Intramolecular Hydroxyalkylation of 4-(3-Hydroxyphenyl)alkanoates[1]

Giuseppe Guanti,* Luca Banfi, and Renata Riva

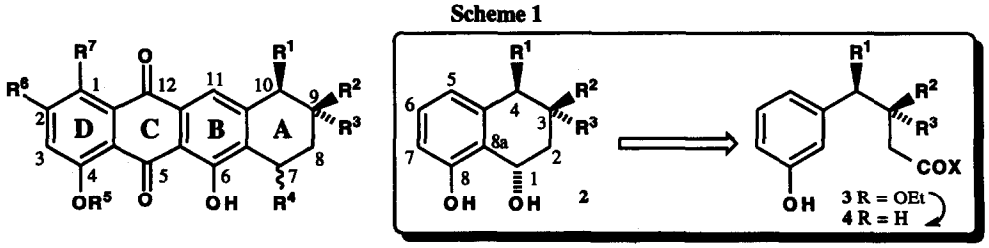
Istituto di Chimica Organica dell'Università degli Studi di Genova, e C.N.R., Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, corso Europa 26, I-16132 GENOVA (Italy)

Abstract: A series of 4-(3-hydroxyphenyl)butanoates **3** has been prepared and transformed into 1,8-dihydroxytetralins of general formula **2** by treatment with 2 equivalents of DIBALH followed by quenching with aqueous NH_4Cl. A possible mechanism for this novel totally regioselective intramolecular hydroxyalkylation is suggested and the factors affecting the stability of 1,8-dihydroxytetralins **2** are also discussed.

Many natural products belonging to the anthracycline family are characterized by the presence of a tetralin system bearing three hydroxy or alkoxy groups at positions 4, 6, 7. Some of them, like Adriamycin and Aklacinomycin A, are well known antitumoral agents and are largely employed for clinical purposes. Many efforts have been made for synthesizing the aglycones of these products and three main rethrosynthetic strategies can be envisaged:[2] a) formation of ring C by coupling ring D with a preformed AB synthon, usually by employing Friedel-Crafts reactions; b) assemblage of ring B by coupling a preformed DC synthon with ring A, often *via* a Diels-Alder cycloaddition; c) construction of ring A as last stage starting from the preformed anthracycline ring system DCB (in this case Marschalk reaction has been widely used[2a]).

For the synthesis of 11-deoxy derivatives, like Aklavinone **1a**, Auramycinone **1b**, 11-Deoxydaunomycinone **1c**, and Menogarol **1d**, the different substitution at C-11 and C-6 determines a lower symmetry of the whole system and this fact has required the development of regioselective transformations for the correct assemblage of rings A and B. Few years ago, in connection with our project on

Scheme 1



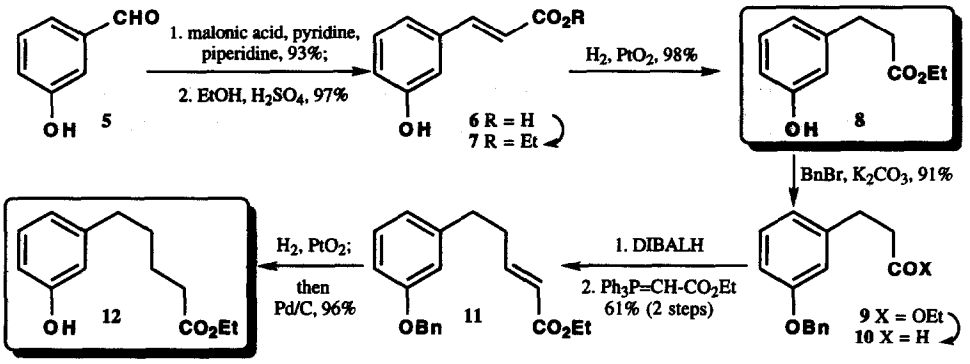
1a: Aklavinone: $R^1 = CO_2Me$; $R^2 = Et$; $R^3 = OH$; $R^4 = \alpha$-OH; $R^5 = R^6 = R^7 = H$

1b: Auramycinone: $R^1 = CO_2Me$; $R^2 = Me$; $R^3 = OH$; $R^4 = \alpha$-OH; $R^5 = R^6 = R^7 = H$

1c: 11-Deoxydaunomycinone: $R^1 = R^6 = R^7 = H$; $R^2 = COCH_3$; $R^3 = OH$; $R^4 = \alpha$-OH; $R^5 = Me$

1d: Menogarol: $R^1 = R^5 = H$; $R^2 = OH$; $R^3 = Me$; $R^4 = \beta$-OMe; $R^6 = R$; $R^7 = OR$

Scheme 2



the synthesis of new antibiotics and other bioactive molecules,[3] we started to be interested in the chemistry of 11-deoxyanthracyclinones. In particular, we focused our attention on the above mentioned strategy a) and, after surveying the various procedures used for the construction of the AB system, we decided to explore a novel route whose strategy is evidenced by the disconnection depicted in Scheme 1. The crucial point of this idea is the feasibility of an *ortho* controlled intramolecular hydroxyalkylation starting from aldehydes **4**,[2b,4] which, on the other hand, would be expected to undergo, for steric reasons, a preferential *para* cyclization when subjected to a ring closure reaction.[5]

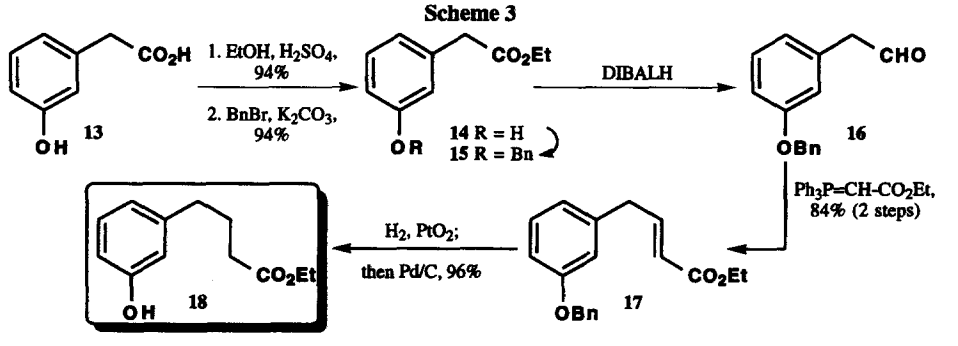
For this purpose we decided to prepare a series of 4-(3-hydroxyphenyl)butanoates **3**, as well as some other model esters like 3-(3-hydroxyphenyl)propanoate **8** and 5-(3-hydroxyphenyl)pentanoate **12** and to reduce them to the corresponding aldehydes, in order to study the factors controlling the *ortho*/*para* ratio in the intramolecular hydroxyalkylation reactions. The results of this studies are herein reported.

Synthesis of the esters.

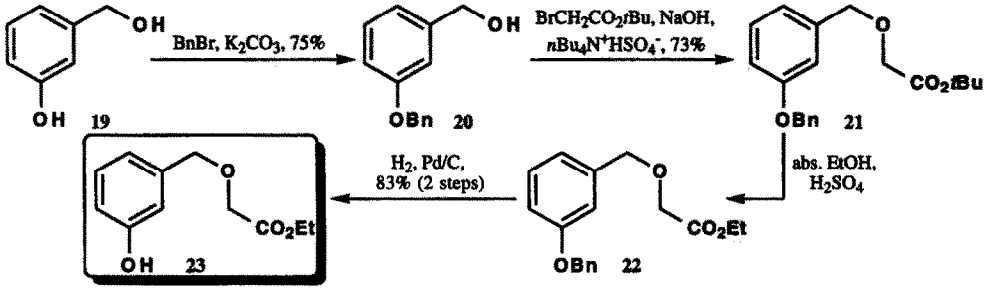
Scheme 2 and 3 show the synthesis of unsubstituted ω-(3-hydroxyphenyl)alkanoates **8**, **12** and **18**, having respectively an aliphatic chain of 3, 5, and 4 atoms. 3-Arylpropanoate **8** was obtained utilizing a Knoevenagel condensation (Scheme 2) between 3-hydroxybenzaldehyde and malonic acid, as reported in literature, to give the α,β-unsaturated acid **6**.[6] The esterification under classical conditions, followed by catalytic hydrogenation furnished compound **8** in high yield. The preparation of the two carbon homologated ester **12** was realized from **8** (Scheme 2) *via* benzylation, reduction with DIBALH of ester **9**[7] and reaction of aldehyde **10** with a stabilized phosphorane.[8] Removal of the benzyl group from α,β-unsaturated ester **11** and hydrogenation of the double bond gave **12** in nearly quantitative yield.

Ethyl 4-(3-hydroxyphenyl)butanoate **18** was prepared from commercially available

Scheme 3



Scheme 4



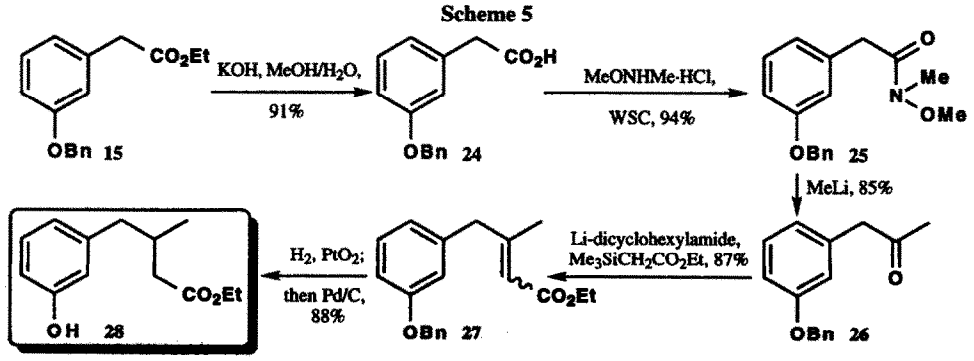
3-hydroxyphenylacetic acid **13**, whose ester was benzylated and transformed into the aldehyde **16** as described in Scheme 3. A two carbon homologation[9] and a reduction/deprotection sequence, identical with the ones reported above for ester **12**, transformed **16** into **18**.

The preparation of an oxa-analogue of **18**, that is **23** (Scheme 4), was performed starting from commercially available 3-hydroxybenzyl alcohol, which was regioselectively benzylated at the phenolic group, using powdered anhydrous potassium carbonate as base. The elongation of **20** was realized using *t*-butyl bromoacetate under phase-transfer conditions.[10,11] The transesterification of **21** under acid catalysis,[12] followed by hydrogenolysis of the benzyl group gave compound **23** in good overall yield.

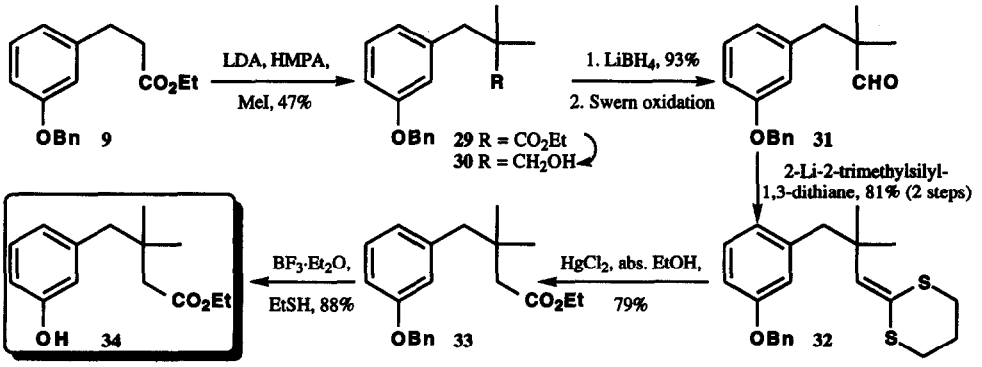
We then turned our attention to 3-substituted-4-(3-hydroxyphenyl)butanoates. First we chose to prepare the 3-monomethyl and the 3,3-dimethyl derivatives of **18**. The preparation of ester **28** was performed starting from the above described benzyl ether **15** *via* Weinreb's N-methoxy amide **25**,[13] which was prepared in an excellent yield (94%) by using a water soluble carbodiimide, that is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, as coupling agent between the acid **24** and N,O-dimethyl hydroxylamine.[14,15,16] The conversion of **25** into the ketone **26** was readily achieved by reacting the former with MeLi.[17,18] The olefination of carbonyl compound **26** was realized using a Peterson-like reaction, as described by Yamamoto.[19] α,β-Unsaturated ester **27** (as a 62 : 38 *E*/*Z* mixture) was finally hydrogenated to furnish the monomethyl derivative **28**.

The synthesis of **34** (Scheme 6) was quite troublesome. First we tried to use **27** as precursor. However, all our efforts for accomplishing the conjugated addition of a methyl group to the unsaturated ester **27** failed[20] and we had to choose a completely new synthetic strategy able to introduce both the geminal methyl groups at an early stage of the synthesis. We used **9** as starting material, which was dialkylated under conditions that are known to minimize autocondensation reactions of the substrate.[21] After various attempts, the homologation of this ester[22,23] was successfully accomplished *via* ketene dithioacetal **32**, obtained from the

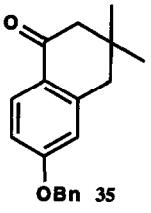
Scheme 5



Scheme 6

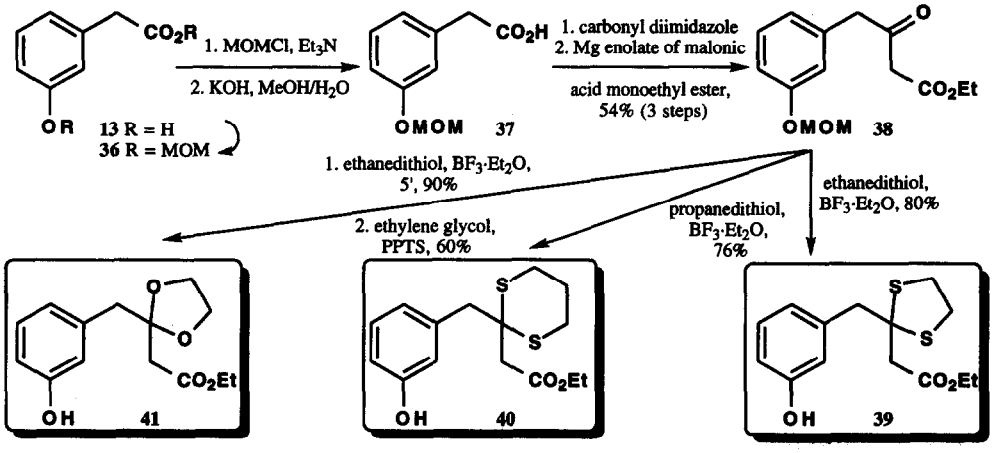


condensation between aldehyde **31** and the lithium anion of commercially available 2-trimethylsilyl-1,3-dithiane.[24] The transformation of **32** into **33** was realized in a one-pot sequence, using $HgCl_2$ in absolute ethanol at room temperature. It is noteworthy that the use of aqueous ethanol at reflux, as usually described[25] for the transformation of ketene dithioacetals into the corresponding ethyl esters, furnished in this case considerable amounts of tetralone **35**, probably arising from an intramolecular Hg(II)-catalyzed Friedel-Crafts acylation of the intermediate carboxylic acid. Finally, the deprotection of phenolic group of **33** with $BF_3{\cdot}Et_2O$ in the presence of ethanethiol[26] gave **34** with 88% yield.

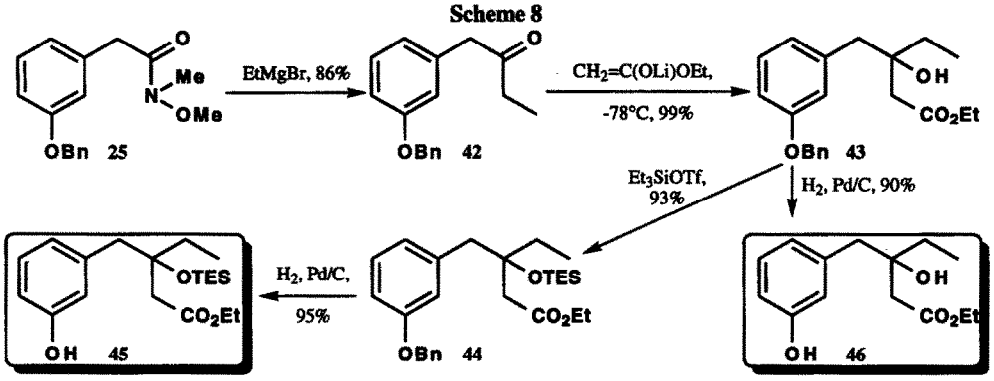


Then we prepared the protected 4-(3-hydroxyphenyl)-3-oxobutanoates **39**, **40**, **41** bearing respectively 1,3-dithiolane, 1,3-dithiane and 1,3-dioxolane as ketone protecting groups. These intermediates are particularly interesting from a synthetic point of view, since they possess, in masked form, a carbonyl function which can be the precursor of the tertiary alcohol of Aklavinone **1a**. The preparation of these compounds was realized through a short reaction sequence starting from acid **13**, as described in Scheme 7. By treatment of **13** with an excess of methoxymethyl chloride and basic hydrolysis of the ester **36**, the acid **37** was obtained. This compound was directly homologated,[27] after its *in situ* transformation into the corresponding imidazolide. The carbonyl group was then readily protected either as thioketal by reaction with the corresponding dithiol, catalyzed by $BF_3{\cdot}Et_2O$[28] or as ketal by reaction with ethylene glycol catalyzed by pyridinium *p*-toluenesulfonate.[29] In the case of the thiols the MOM protecting

Scheme 7



Scheme 8



group was also removed under these reaction conditions, while in the case of the ketal it has to be removed previously.

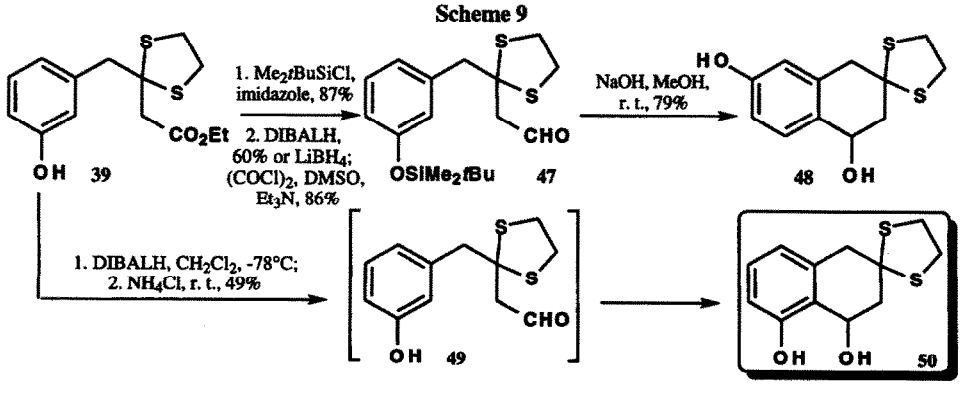
The preparation of racemic **45** and **46**, two intermediates bearing the same substituents of Aklavinone in position 3, was accomplished starting from **25**, which was readily transformed into the ethyl ketone **42** (Scheme 8). The reaction of the latter with the lithium enolate of ethyl acetate gave the tertiary alcohol **43**, which was transformed into **44** by protection of the tertiary alcoholic group as triethylsilyl ether.[28,30] Finally, catalytic debenzylation of the phenolic group of both **43** and **44** gave **46** and **45** respectively.

Reduction of the esters.

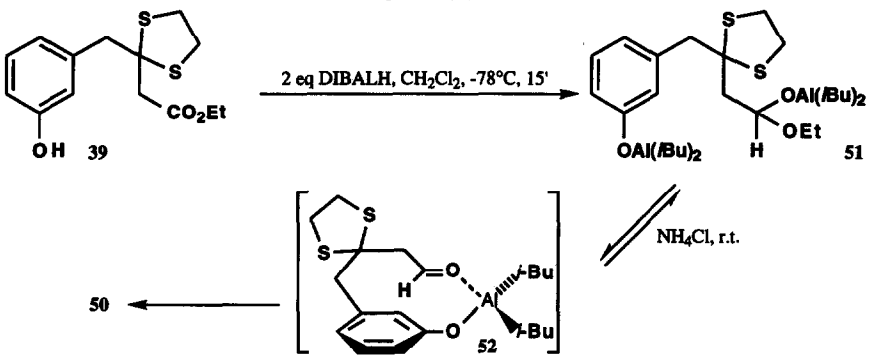
Since we were particularly interested in the preparation of aldehyde **49**, we first studied the reduction of ester **39**, by treating it with DIBALH under conditions generally used for obtaining an aldehyde from an ester. However, although **39** disappeared, we could isolate only traces of aldehyde **49**. Supposing that the free phenolic group could be in some way responsible for this unsuccessful result, we decided to protect the hydroxy group before subjecting the ester to the reduction. Actually, when the TBDMS protected ester derived from **39** (Scheme 9) was treated with DIBALH the corresponding aldehyde **47** was obtained.[31] Nevertheless when we tried to restore the free phenolic group from **47** with *n*-$Bu_4N^+F^-$ in tetrahydrofuran, only traces of aldehyde **49** were formed, the major products arising from decomposition side reactions.

On the other hand, treatment of **47** with methanolic sodium hydroxide quickly restored the phenolic hydroxy group, but the resulting aldehyde **49** could not be isolated since it immediately cyclized under basic conditions to give 1,6-dihydroxytetralin **48**, resulting from an intramolecular hydroxyalkylation reaction exclusively in the position *para* to the phenolic OH.

Scheme 9



Scheme 10



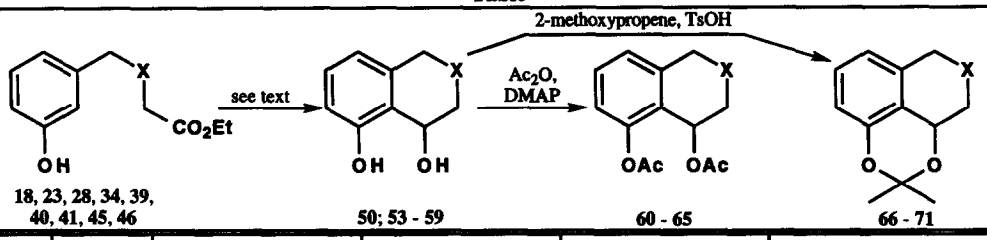
At this point we decided to re-examine more in detail the previously studied reduction of unprotected **39** with DIBALH, trying to separate and characterize the reaction products. A column chromatography of the reaction mixture was performed and three other products were isolated besides the small amount of aldehyde **49**: some unreacted ester **39**, a primary alcohol derived from further reduction of the intermediate aldehyde[32] and, as major product, a secondary alcohol, whose structure, after ^1H and ^{13}C n.m.r. analyses, appeared to be, to our surprise, that of the 1,8-dihydroxytetralin **50**. A definitive confirmation of the structure of this compound came by its transformation into the corresponding *iso*-propylidene derivative, when it was treated with 2-methoxypropene, with acid catalysis. It is noteworthy that, while in ^1H n.m.r. spectrum of the crude reaction mixture we could detect only little amount of aldehyde **49**, we did not find even traces of **48**.

Stimulated by this unexpected result we decided to study this reaction in more detail and performed many experiments in order to improve the yields and to better understand the mechanism of formation of **50**. The best way to minimize side reactions is a short reaction time with DIBALH (15 min) at a carefully controlled temperature (-78°C). Quenching also is crucial: actually, working in slightly basic (that is just addition of water to the reaction mixture) or acidic (acetic acid) conditions gave in both cases a completely decomposed mixture, while quenching with saturated aqueous ammonium chloride solution, which displays a buffer activity, gave considerably better yields.

We verified also that the transformation of the aldehyde into the 1,8-dihydroxytetralin is not immediate, but requires a variable reaction time, best yields being obtained after stirring the quenched heterogeneous mixture at room temperature for about 6 hours. Moreover, if the aluminium salts were removed soon after quenching with NH_4Cl the yield again was lower. For the final work-up, the addition of saturated solution of Rochelle's salt were the conditions of choice, while using hydrochloric acid the overall yields dramatically dropped down. This fact is due to the somewhat instability of diol **50** under acidic conditions (*vide infra*). Yields were thus furtherly optimized by *in situ* converting **50** into the corresponding diacetate.

An interpretation of the formation of **50** and most of all of the factors responsible for the high regioselectivity of this novel cyclization reaction can be envisaged, the rationale being in part supported by experimental and literature data.[33] Of the two equivalents of DIBALH required to carry out this reaction, it is likely that the first one reacts with the phenol giving the diisobutylaluminium phenolate and that it is the second one which is really involved in the reduction of the ester function. The most likely intermediate should be an O-(diisobutylaluminium) acetal **51** (Scheme 10), which probably can not evolve under the used reaction conditions. Aqueous quenching (best conditions use saturated aqueous NH_4Cl) probably produces free aldehyde function, which finally react to give product **50**. Interestingly, when the mixture deriving from treatment of **39** with DIBALH was quenched with $NaBH_4$/MeOH, either at -78°C or after warming up to 0°C, no cyclized product **50** was isolated, the main product being the acyclic primary alcohol. This fact suggest that the cyclization takes place only after aqueous quenching.

Table



18, 23, 28, 34, 39, 40, 41, 45, 46 — 50; 53 - 59 — 60 - 65 — 66 - 71

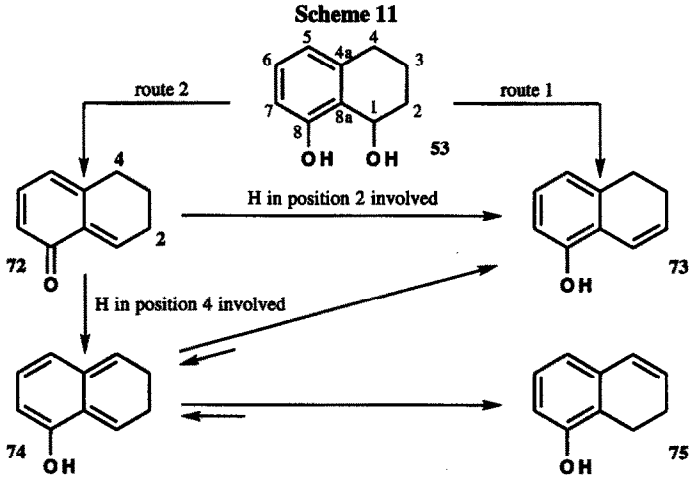
Entry	Starting ester	X	Yield of diol[a]	Yield of diacetate (from ester)[b]	Yield of isopropyliden derivative (from ester)
1	**18**	$-CH_2-$	10% (13%) [**53**]	10% (18%) [**60**]	2% [**66**]
2	**23**	-O-	8% [**54**]	not det.	not det.
3	**28**	$-CH(CH_3)-$	not det. [**55**][c]	38% (52%) [**61**]	8% [**67**]
4	**34**	$-C(CH_3)_2-$	65% (69%) [**56**]	60% (64%) [**62**]	55% [**68**]
5	**39**		42% (49%) [**50**]	54% (75%) [**63**]	40% [**69**]
6	**40**		32% [**57**]	40% (54%) [**64**]	40% [**70**]
7	**41**		47% (52%) [**58**]	not det.	not det.
8	**45**	$>C(OTES)CH_2CH_3$	56% (64%) [**59**][d]	43% (58%) [**65**]	40% [**71**]
9	**46**	$>C(OH)CH_2CH_3$	no reaction	/	/

NOTE : **a)** yield from not recovered ester are in brackets; **b)** yield from not recovered O-acetylated ester are in brackets; **c)** **55** was obtained as an approximately 1:1 diastereomeric mixture; **d)** **59** was obtained as a 77 : 23 diastereomeric mixture (determined by ^{1}H-n.m.r).

The high regioselectivity of the reaction can be explained if we suppose the formation of a chelated intermediate like **52**: the formation of a covalent bond between the aluminium reagent and the phenolic group produces an intermediate in which the aluminium atom can also act as Lewis acid with respect to the carbonyl group of the aldehyde, as soon as this function is released by aqueous quenching. In this hypothesis a six-membered cyclic transition state is possible and its evolution leads to the *ortho* cyclized product. The formation of a chelated intermediate has been demonstrated in the last years in extended studies on the *ortho*-directed intermolecular acylations and hydroxyalkylation of phenols, catalyzed by different Lewis acids,[33] although those reactions were always performed under anhydrous conditions. In our case it is more difficult to prove the real structure of the intermediate on which the cyclization occurs: species **52** seems to be the most likely because it could explain the high regioselectivity of the hydroxyalkylation process. On the other hand, when the cyclization reaction was carried out under basic conditions and in the presence of a metal unable to promote chelation (sodium) the only product isolated was **48**, derived from the attack in the *para* position, probably favoured for steric reasons.

The scope and limitations of this reaction were tested on other 4-(3-hydroxyphenyl)butanoates, differently substituted in position 3 and on ethyl 3-(3-hydroxyphenyl)propanoate **8** and ethyl 5-(3-hydroxyphenyl)pentanoate **12**, as summarized in the Table. All butanoates, with the exception of **46**, which did not react even in the presence of a large excess of DIBALH, gave the corresponding cyclization products, although with variable yields.[34] The other two esters, that is **8** and **12**, gave only the stable corresponding

Scheme 11



aldehydes. About the 1,8-dihydroxytetralins obtained a general trend can be emphasized: the yield seems to depend dramatically upon the substitution in position 3 by respect to the ester function. Actually, compounds **18** and **23** gave **53** and **54** respectively in very low yield (about 10%), while cyclization product **55**, derived from **28**, has been isolated with appreciable yield only as the diacetate **61** (38%); especially for compound **18** we observed the formation of many not identifiable by-products. On the contrary, compounds **50**, **56**, **57**, **58**, **59** have been obtained in moderate to good yields (between 32 and 69%), which usually have been improved by isolating them as diacetates.

From these data it seems that the higher is the substitution at the γ position of the ester the higher is the amount of 1,8-dihydroxytetralin isolated. Thus the best results were achieved when carbon 3 of the aliphatic chain was quaternary. A possible explanation of this outcome could be given by considering the structures of the compounds obtained by cyclization and their stability under the reaction conditions. It is likely that the 1,8-dihydroxytetralin, once formed, undergo a water elimination either between position 1 and 2 (route 1) or through an *o*-quinone methide intermediate (route 2), to give dihydronaphthols **73**, **74**, **75** (Scheme 11) and that the rates of these decompositions are stongly depending on substitution in position 3. The propensity of 2-hydroxybenzyl alcohols to undergo elimination reactions to give an *o*-quinone methide is quoted in the literature;[35] on the other hand the possible formation of quinone methide intermediates during reduction reactions and most likely *in vivo*, during the action of Daunomycin and other anthracycline analogues, has been recently demonstrated.[36]

With the purpose of better understanding the effects of substituents on the stability of 1,8-dihydroxytetralins we performed some empirical calculations using an MM2 program (CSC Chem 3D Plus™). Preliminary results seem to indicate that the preferred conformation of the aliphatic ring is, as usual in these systems,[37] a half-chair, in some cases more similar to envelope, depending upon the substituents. Thus the hydroxy group at C-1 rapidly interconverts between a pseudoequatorial and a pseudoaxial position. Our calculations have shown that in all cases examined, the pseudoaxial conformation has the higher steric energy with dihedral angles [OH(1)-C_1-C_2-H(2)] in the range between 146.4° and 163.5°. However, only in compounds tetrasubstituted in position 3 the difference in the steric energy of the two conformations is appreciable, determining a low contribution of the conformer with the pseudoaxial OH. On the other hand for 3-unsubstituted compound, most of all for compound **53**, the difference in steric energy of the two conformers is very low and, in this case, both give a significant contribution. It's likely that the elimination processes are favoured in 'pseudoaxial conformers' (see also dihedral angles), in which the C-O bond to be broken is perpendicular to the aromatic ring. This fact could justify the propensity of some compounds to give side

reactions.

The application of this new reaction to more complex substrates has been recently verified and published by us, also on chiral substrates.[38] Further elaboration of this strategy is also in progress in our laboratories.

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 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). Tlc 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 s were measured after an elution of 7-9 cm. Chromatographies were carried out on 70-230 mesh silica gel using the "flash" methodology.[39] 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.

3-(3-Hydroxyphenyl)-2-propenoic acid 6. This compound was prepared according to ref. 4, starting from 3-hydroxybenzaldehyde **5** and was obtained in 93% yield as a white solid. Anal. found C, 65.65; H, 4.95. $C_9H_8O_3$ requires C, 65.85; H, 4.91. ^1H n.m.r.(acetone-d_6): δ 6.46 [1H, d, ArCH=C*H*CO_2H, J=16.0]; 6.92 [1H, ddd, *H* ortho to -OH and para to the chain, J=7.9, 2.5, 1.2]; 7.12-7.19 [2H, m, *H* para to -OH & *H* ortho to both the substituents]; 7.28 [1H, t, *H* meta to -OH, J=7.8]; 7.61 [1H, d, ArC*H*=CHCO_2H, J=16.0].

Ethyl 3-(3-hydroxyphenyl)-2-propenoate 7. Concentrated sulphuric acid (2 ml, 37.55 mmol) was added to a solution of **6** (9.93 g, 60.55 mmol) in absolute ethanol (150 ml, 2.57 mol) and the mixture refluxed for 7 hrs. The solvent was removed under reduced pressure and the residue diluted with water and neutralized with solid $NaHCO_3$. After extraction with Et_2O, the combined organic extracts were washed with saturated $NaHCO_3$. Evaporation of the solvent gave crude **7** as a colourless oil, pure enough for further reactions (single spot in tlc, 11.28 g, 97%). R_f 0.47 (PE : Et_2O 1:1). ^1H n.m.r.: δ 1.34 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 4.28 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.30 [1H, broad s, -O*H*]; 6.41 [1H, d, ArCH=C*H*CO_2Et, J=16.0]; 6.87 [1H, ddd, *H* ortho to -OH & para to the chain, J=8.1, 2.5, 1.0]; 7.02 [1H, t, *H* ortho to both the substituents, J=1.9]; 7.10 [1H, broad d, *H* para to -OH, J=7.7]; 7.27 [1H, t, *H* meta to OH, J=7.8]; 7.64 [1H, d, ArC*H*=CH-, J=16.0].

Ethyl 3-(3-hydroxyphenyl)propanoate 8. PtO_2 (305 mg) was added to a solution of **7** (5.85 g, 30.43 mmol) in EtOH 96% (150 ml) and the mixture was hydrogenated for 20 hrs at r. t.. The catalyst was filtered off and washed with EtOH. After solvent removal crude product was chromatographed (PE : Et_2O 7:3 → 6:4) to give pure **8** as a colourless oil (5.77 g, 98%). R_f 0.52 (PE : Et_2O 1:1). Anal. found C, 68.25; H, 7.40. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27. ^1H n.m.r.: δ 1.24 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 2.61 [2H, centre of m, -CH_2CO_2Et]; 2.91 [2H, t, ArCH_2-, J=7.7]; 4.14 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 4.89 [1H, s, -O*H*]; 6.64-6.70 [2H, m, *H* ortho to -OH]; 6.78 [1H, broad d, *H* para to -OH, J=7.3]; 7.12 - 7.20 [1H, m, *H* meta to -OH].

Ethyl 3-[3-(benzyloxy)phenyl]propanoate 9. A solution of **8** (4.88 g, 25.12 mmol) in anhydrous DMF (30 ml) was treated with K_2CO_3 (8.68 g, 62.80 mmol) and stirred at r.t. for 15 min. Benzyl bromide (7.47 ml, 62.80 mmol) was added and the mixture warmed at 80°C for 1 day. The reaction mixture was diluted with water and the pH adjusted at 4 with 5% aqueous $NH_4H_2PO_4$. After extraction with Et_2O and solvent removal

the crude product was chromatographed (PE : Et_2O 9:1 → 1:1) to give **9** as a colourless oil (6.50 g, 91%). R_f 0.48 (PE : Et_2O 8:2). Anal. found C, 76.15; H, 7.30. $C_{18}H_{20}O_3$ requires C, 76.03; H, 7.09. ^1H n.m.r.: δ 1.24 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 2.61 [2H, centre of m, Ar$CH_2CH_2CO_2$Et]; 2.93 [2H, t, ArCH_2-, J=7.7]; 4.13 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.05 [2H, s, -OCH_2Ph]; 6.78 - 6.87 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.16 - 7.48 [6H, m, aromatics of Bn & *H* meta to -OBn].

3-[3-(Benzyloxy)phenyl]propanal 10. A solution of **9** (2.12 g, 7.45 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -78°C and treated with DIBALH (1 M sol. in CH_2Cl_2, 11.17 ml, 11.17 mmol), previously cooled to the same temperature. After 30 min the reaction was quenched with saturated NH_4Cl (10 ml) and the mixture was diluted with Et_2O and 1 M HCl, until a good phase separation was gained. After extraction, combined organic phases were washed with brine until neutral and solvent was removed under reduced pressure. Crude aldehyde was used as such for the next reaction. R_f 0.33 (PE : Et_2O 8:2).

Ethyl (*E*)-5-[3-(benzyloxy)phenyl]-2-pentenoate 11. 100 mg of powdered 4 Å molecular sieves (activated overnight in oven at 250°C) were added to a solution of crude **10** (obtained from 7.45 mmol of **9**) in CH_2Cl_2 (25 ml) and the mixture was stirred at r. t. for 15 min. Then (carbethoxymethylene)triphenylphosphorane (3.89 g, 11.17 mmol) was added. After stirring for 2.5 hrs the reaction mixture was concentrated *in vacuo* and the residue directly chromatographed (PE : Et_2O 9:1 → 8:2) to give **11** as a colourless oil and as a single diastereoisomer (1.42 g, 61% from **9**). R_f 0.50 (PE : Et_2O 8:2). Anal. found C, 77.55; H, 7.10. $C_{20}H_{22}O_3$ requires C, 77.39; H, 7.14. ^1H n.m.r.: δ 1.28 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 2.46 - 2.57 [2H, m, ArCH_2CH_2-]; 2.72 - 2.79 [2H, m, ArCH_2CH_2-]; 4.19 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.06 [2H, s, -OCH_2Ph]; 5.84 [1H, dt, -CH_2CH=C*H*-, J=15.6 (d), 1.5 (t)]; 6.76 - 6.84 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.00 [1H, dt, -CH_2CH=C*H*-, J=15.6 (d), 6.8 (t)]; 7.17 - 7.47 [6H, m, aromatics of Bn & *H* meta to -OBn].

Ethyl 5-(3-hydroxyphenyl)pentanoate 12. 75 mg of PtO_2 were added to a solution of **11** (1.42 g, 4.56 mmol) in EtOH 96% (40 ml) and hydrogenated overnight; then 190 mg of Pd over charcoal (10%) were added and the mixture hydrogenated again for additional 6 hrs. The catalysts were filtered off and washed with EtOH; finally the solution was concentrated *in vacuo*. Chromatography (PE : Et_2O 7:3 → 6:4) gave **12** as a colourless oil (973 mg, 96%). R_f 0.55 (PE : Et_2O 1:1). Anal. found C, 70.40; H, 8.10. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16. ^1H n.m.r.: δ 1.25 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 1.65 [4H, centre of m, -$(CH_2)_2CH_2CO_2$Et]; 2.32 [2H, centre of m, -CH_2CO_2Et]; 2.58 [2H, centre of m, ArCH_2CH_2-]; 4.13 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.88 [1H, s, -O*H*]; 6.63 - 6.65 [2H, m, 2*H* ortho to -OH]; 6.75 [1H, broad d, *H* para to -OH, J=8.0]; 7.10 - 7.19 [1H, m, *H* meta to -OH].

Ethyl (3-hydroxyphenyl)acetate 14. It was prepared by the same procedure reported for compound **7**, starting from 3-hydroxyphenylacetic acid **13** (20.64 g, 135.68 mmol). Crude product was distilled (b.p. 130-140°C, p=$6 \cdot 10^{-2}$ torr, 23.02 g, 94%). R_f 0.49 (PE : Et_2O 1:1). Anal. found C, 66.75; H, 6.85. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71. ^1H n.m.r.: δ 1.26 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 3.57 [2H, s, ArCH_2CO_2Et]; 4.16 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.25 [1H, s, -O*H*]; 6.71 - 6.86 [3H, m, *H* para & 2*H* ortho to -OH]; 7.19 [1H, t, *H* meta to -OH, J=8.0].

Ethyl 3-(benzyloxyphenyl)acetate 15. It was prepared by the same procedure reported for compound **9**, starting from **14** (2.11 g, 11.74 mmol). Chromatography (PE : Et_2O 9:1 → 8:2) furnished **15** as a colourless oil (2.98 g, 94%). R_f 0.73 (PE : Et_2O 1:1). Anal. found C, 75.75; H, 6.80. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71. ^1H n.m.r.: δ 1.25 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 3.58 [2H, s, ArCH_2CO_2Et]; 4.15 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.06 [2H, s, -OCH_2Ph]; 6.85 - 6.96 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.19-7.48 [6H, m, aromatics of Bn & *H* meta to -OBn].

[3-(Benzyloxy)phenyl]ethanal 16. It was prepared by the same procedure reported for compound **10**, starting from **15** (1.34 g, 4.95 mmol). Crude aldehyde was used as such for the next reaction. R_f 0.30 (PE : Et_2O 8:2). ^1H n.m.r.: δ 3.66 [2H, d, ArCH_2CHO, J=2.4]; 5.07 [2H, s, -OCH_2Ph]; 6.81 - 6.96 [3H, m, *H* para & 2*H* ortho

to -OBn]; 7.26-7.46 [6H, m, aromatics of Bn & *H* meta to -OBn]; 9.74 [1H, t, -C*H*O, J=2.4].

Ethyl (*E*)-4-[3-(benzyloxy)phenyl]-2-butenoate 17 It was prepared by the same procedure reported for compound **11**, starting from crude **16** (obtained from 4.95 mmol of **15**). Chromatography (PE : Et_2O 8:2) gave **17** as a colourless oil and as a single diastereoisomer (1.23 g, 84% from **15**). R_f 0.41 (PE : Et_2O 8:2). Anal. found C, 77.15; H, 7.00. $C_{19}H_{20}O_3$ requires C, 77.00; H, 6.80. ^{1}H n.m.r.: δ 1.28 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 3.20 - 3.59 [2H, m, ArCH_2CH=CH-]; 4.18 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.06 [2H, s, -OCH_2Ph]; 5.82 [1H, dt, -CH_2CH=C*H*-, J=15.6 (d), 1.6 (t)]; 6.77 - 6.89 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.08 [1H, dt, -CH_2C*H*=CH-, J=15.6 (d), 6.8 (t)]; 7.20 - 7.48 [6H, m, aromatics of Bn & *H* meta to -OBn].

Ethyl (3-hydroxyphenyl)butanoate 18. It was prepared by the same procedure reported for compound **12**, starting from **17** (2.90 g, 9.81 mmol). Chromatography (PE : Et_2O 1:1) gave **18** as a colourless oil (1.96 g, 96%). R_f 0.51 (PE : Et_2O 1:1). Anal. found C, 69.40; H, 7.95. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74. ^{1}H n.m.r.: δ 1.26 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 1.94 [2H, quintuplet, -C$H_2CH_2CO_2$Et, J=7.5]; 2.32 [2H, t,-$CH_2CH_2CO_2$Et, J=7.5]; 2.61 [2H, t, ArCH_2CH_2-, J=7.5]; 4.13 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.92 [1H, s, O*H*]; 6.66 - 6.76 [3H, m, *H* para & 2*H* ortho to -OH]; 7.15 [1H, dd, *H* meta to -OH, J=7.6, 8.8].

[3-(Benzyloxy)phenyl]methanol 20. It was prepared by the same procedure reported for compound **9**, starting from 3-hydroxybenzyl alcohol **19** (3.07 g, 24.74 mmol). Chromatography (PE : Et_2O 7:3 → 1:1) gave **20** as a colourless oil (3.89 g, 75%). R_f 0.70 (PE : Et_2O 2:8). Anal. found C, 78.40; H, 6.35. $C_{14}H_{14}O_2$ requires C, 78.48; H, 6.59. ^{1}H n.m.r.: δ 1.66 [1H, t, -CH_2O*H*, J=5.8]; 4.68 [2H, d, CH_2OH, J=5.8]; 5.08 [2H, s, -OCH_2Ph]; 6.88 - 7.03 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.24 - 7.46 [6H, m, aromatics of Bn & *H* meta to -OBn].

***t*-Butyl 4-[3-(benzyloxy)phenyl]-3-oxabutanoate 21.** A solution of **20** (204 mg, 0.952 mmol) in benzene (5 ml) was treated with 50% aqueous NaOH (1 ml), *t*-butyl bromoacetate (230 µl, 1.425 mmol) and *n*-$Bu_4N^+HSO_4^-$ (16 mg, 47 µmol); the resulting mixture was stirred overnight at r.t.. The reaction was diluted with brine and Et_2O, the pH was adjusted to 7 with 6 N HCl. Finally, extraction with Et_2O and solvent removal, followed by chromatography (PE : Et_2O 9:1) gave **21** as a colourless oil (229 mg, 73%). R_f 0.44 (PE : Et_2O 8:2). Anal. found C, 73.35; H, 7.35. $C_{20}H_{24}O_4$ requires C, 73.15; H, 7.37. ^{1}H n.m.r.: δ 1.49 [9H, s, -$CO_2C(CH_3)_3$]; 3.98 [2H, s, -OCH_2CO_2*t*-Bu]; 4.60 [2H, s, ArCH_2OCH_2-]; 5.08 [2H, s, -OCH_2Ph]; 6.88 - 7.06 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.23 - 7.48 [6H, m, aromatics of Bn & *H* meta to -OBn].

Ethyl 4-[3-(benzyloxy)phenyl]-3-oxabutanoate 22. A solution of **21** (2.00 g, 6.10 mmol) in absolute EtOH (18 ml) was treated with concentrated H_2SO_4 (195 µl, 3.66 mmol) and heated at reflux for 2 hrs. The solution was concentrated under reduced pressure, diluted with water and extracted with Et_2O. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$ and brine. The solvent was removed and crude **22** used as such in the next reaction. R_f 0.27 (PE : Et_2O 8:2). ^{1}H n.m.r.: δ 1.29 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 4.08 [2H, s, -OCH_2CO_2Et]; 4.23 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 4.62 [2H, s, ArCH_2OCH_2-]; 5.08 [2H, s, -OCH_2Ph]; 6.89 - 7.03 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.23 - 7.46 [6H, m, aromatics of Bn &*H* meta to -OBn].

Ethyl 4-(3-hydroxyphenyl)-3-oxabutanoate 23. 350 mg of Pd over charcoal (10%) were added to a solution of crude **22** (obtained from 6.10 mmol of **21**) in 96% EtOH (50 ml) and the mixture was hydrogenated for 1.5 hrs. The catalyst was filtered off and the solution was concentrated under reduced pressure. Chromatography (PE : Et_2O 6:4 → 1:1) gave **23** as a colourless oil (1.06 g, 83% from **21**). R_f 0.32 (PE : Et_2O 6:4). Anal. found C, 62.65; H, 6.55. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.71. ^{1}H n.m.r.: δ 1.29 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 4.10 [2H, s, -OCH_2CO_2Et]; 4.24 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.59 [2H, s, ArCH_2OCH_2-]; 5.17 [1H, s, -O*H*]; 6.79 [1H, ddd, *H* ortho to -OH & para to the side chain, J=8.0, 2.6, 1.1], 6.88 - 6.93 [2H, m, *H* para & *H* ortho to -OH and side chain]; 7.22 [1H, t, *H* meta to -OH, J=7.4].

[3-(Benzyloxy)phenyl]acetic acid 24. Ester **15** (6.37 g, 23.56 mmol) was treated with a solution of KOH (2.25 g, 40.07 mmol) in a mixture of MeOH : H_2O 9:1 (60 ml) and stirred at r.t. for 6 hrs. The reaction was diluted with Et_2O and extracted twice with small portions of Et_2O. The aqueous solution was then acidified until pH 2 with 1 N HCl and saturated with NaCl. Extraction with Et_2O gave, after solvent removal, acid **24** (5.20 g, 91%), which was directly used for the next reaction.

Methyl 2-[3-(benzyloxy)phenyl]-N-methyl acetohydroxamate 25. A solution of crude **24** (from 12.39 mmol of ester **15**) in THF (25 ml) was treated with N,O-dimethylhydroxylamine hydrochloride (2.05 g, 21.06 mmol) dissolved in water (25 ml) and the pH was adjusted to 4.5 with 1 N NaOH. A solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC, 6.79 g, 30.97 mmol) in water (85 ml) was added dropwise over a period of 25 min to the solution of **24** and N,O-dimethylhydroxylamine, while the pH was mantained to a constant value of 4.5. After 2.5 hrs the solution was saturated with NaCl and extracted with EtOAc; finally, the solvent was removed under reduced pressure. Chromatography (PE : EtOAc 6:4 → 4:6) gave pure **25** (3.32 g, 94%). R_f 0.39 (PE : EtOAc 7:3 with 10% MeOH). Anal. found C, 71.40; H, 6.75; N, 4.80. $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91. ^{1}H n.m.r.: δ 3.19 [3H, s, -N(OCH$_3$)C*H*$_3$]; 3.57 [3H, s, -N(OC*H*$_3$)CH$_3$]; 3.74 [2H, s, ArC*H*$_2$CO-]; 5.06 [2H, s, -OC*H*$_2$Ph]; 6.83 - 6.96 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.19 - 7.48 [6H, m, aromatics of Bn & *H* meta to -OBn].

[3-(Benzyloxy)phenyl]acetone 26. A solution of **25** (3.32 g, 11.65 mmol) in anhydrous THF (25 ml) was cooled to -78°C and treated with MeLi (14.6 ml of 1.6 M solution in Et_2O, 23.30 mmol). After 1.25 hrs the reaction was quenched with saturated aqueous NH_4Cl solution. Extraction with Et_2O and solvent removal *in vacuo* gave crude **26**. Chromatography (PE : Et_2O 8:2 → 1:1) gave pure **26** (2.38 g, 85%). R_f 0.41 (PE : Et_2O 7:3). Anal. found C, 79.65; H, 6.70. $C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71. ^{1}H n.m.r.: δ 2.13 [3H, s, -COC*H*$_3$]; 3.66 [2H, s, ArC*H*$_2$CO-]; 5.06 [2H, s, -OC*H*$_2$Ph); 6.79 - 6.94 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.21 - 7.48 [6H, m, aromatics of Bn & *H* meta to -OBn].

Ethyl 4-[3-(benzyloxy)phenyl]-3-methyl-2-butenoate 27. Ethyl trimethylsilylacetate (3.62 ml, 19.80 mmol) was added dropwise to a 0.4 M solution of lithium dicyclohexylamide (prepared as described in ref. 16, 49.5 ml, 19.80 mmol)), previously cooled to -78°C. After 10 min a solution of **26** (2.38 g, 9.90 mmol) in anhydrous THF (10 ml) was added to the solution and the temperature was allowed to rise to -50°C. After 2 hrs the reaction was quenched with saturated aqueous NH_4Cl (5 ml). The mixture was filtered over a celite pad and then extracted with EtOAc. After solvent removal crude **27** was chromatographed (PE : Et_2O 9:1 → 8:2) to give a colourless oil (2.67 g, 87% of a mixture of diastereoisomer; diastereomeric ratio: 68:32 (*Z*/*E*) determined by ^{1}H n.m.r.). The two diastereoisomers were not separated. R_f 0.56 (*E*), 0.62 (*Z*) (PE : Et_2O 8:2). ^{1}H n.m.r.: diastereoisomer *Z* δ 1.29 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.1]; 1.78 [3H, d, -C(C*H*$_3$)=CH-, J=1.3]; 3.99 [2H, s, ArC*H*$_2$C(CH$_3$)=]; 4.19 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.1]; 5.04 [2H, s, -OC*H*$_2$Ph]; 5.77 [1H, centre of m, -C(CH$_3$)=C*H*]; 6.76 - 6.87 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.15 - 7.47 [6H, m, aromatics of Bn & *H* meta to -OBn]; diastereoisomer *E* δ 1.28 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.1]; 2.11 [3H, d, -C(C*H*$_3$)=CH-, J=1.3]; 3.39 [2H, s, ArC*H*$_2$C(CH$_3$)=]; 4.15 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.1]; 5.05 [2H, s, -OC*H*$_2$Ph]; 5.69 [1H, q, -C(CH$_3$)=C*H*, J=1.3]; 6.76 - 6.87 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.15 - 7.47 [6H, m, aromatics of Bn & *H* meta to -OBn].

Ethyl 4-(3-hydroxyphenyl)-3-methylbutanoate 28. It was prepared by the same procedure reported for compound **12**, starting from **27** (221 mg, 712 μmol). Chromatography (PE : Et_2O 7:3 → 65:35) gave **28** as a colourless oil (139 mg, 88%). R_f 0.30 (PE : Et_2O 7:3). Anal. found C, 70.40; H, 8.35. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16. ^{1}H n.m.r.: δ 0.94 [3H, d, -CH(C*H*$_3$)-, J=6.4]; 1.25 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.1]; 2.10 - 2.79 [5H, m, ArC*H*$_2$C*H*(CH$_3$)C*H*$_2$CO$_2$Et]; 4.12 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.1]; 5.02 [1H, s, -O*H*]; 6.60 - 6.76 [3H, m, *H* para & 2*H* ortho to -OH]; 7.13 [1H, dt, *H* meta to -OH, J=7.6 (t), 1.1 (d)].

Ethyl 3-[3-(benzyloxy)phenyl]-2,2-dimethylpropanoate 29. A solution of **9** (221 mg, 777 μmol) in anhydrous THF was cooled to -78°C; then a 0.4 M solution of LDA (2.91 ml, 1.17 mmol) in THF : *n*-hexane 75:25, previously cooled to the same temperature was added and the solution stirred for 30 min. HMPA (68

µl, 388 µmol) and iodomethane (73 µl, 1.17 mmol) were added and the mixture stirred for 45 min. The reaction was treated with additional LDA (3.88 ml, 1.55 mmol) in THF and, after 20 min, with a second portion of HMPA (68 µl, 388 µmol) and iodomethane (96 µl, 1.55 mmol). Finally, after 15 min, the reaction was quenched with saturated aqueous NH_4Cl (5 ml) and the pH was adjusted to 8 by careful addition of 1 N HCl. After extraction with Et_2O, the combined organic phases were evaporated to dryness. Chromatography (PE : Et_2O 95:5 → 1:1) gave pure **29** as a colourless oil (115 mg, 47%), together with variable amounts of autocondensation products of starting **9**. R_f 0.44 (PE : Et_2O 9:1). Anal. found C, 76.65; H, 7.50. $C_{20}H_{24}O_3$ requires C, 76.89; H, 7.74. ^{1}H n.m.r.: δ 1.16 [6H, s, -C(CH_3)$_2$$CO_2$Et]; 1.23 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 2.82 [2H, s, ArCH_2-]; 4.10 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.04 [2H, s, -OCH_2Ph]; 6.70 - 6.85 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.16 [1H, t, *H* meta to -OBn, J=7.9]; 7.30 - 7.44 [5H, m, aromatics of Bn].

3-[3-(Benzyloxy)phenyl]-2,2-dimethyl-1-propanol 30. A solution of **29** (1.01 g, 3.25 mmol) in anhydrous Et_2O (40 ml) was cooled to 0°C and treated with $LiBH_4$ [298 mg(95%), 13.00 mmol, added in two portions]. The mixture was allowed to react at r.t. over a period of 24 hrs. The reaction was quenched with NH_4Cl (10 ml) and extracted with Et_2O. After solvent removal, chromatography (PE : Et_2O 7:3) gave pure **30** (835 mg, 93%). R_f 0.25 (PE : Et_2O 7:3). Anal. found C, 79.85; H, 8.30. $C_{18}H_{22}O_2$ requires C, 79.96; H, 8.20. ^{1}H n.m.r.: δ 0.87 [6H, s, -C(CH_3)$_2$$CH_2$OH]; 1.26 [1H, broad s, -O*H*]; 2.54 [2H, s, ArCH_2-]; 3.27 [2H, s, -CH_2OH]; 5.08 [2H, s, -OCH_2Ph]; 6.75 - 6.87 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.19 [1H, broad t, *H* meta to -OBn, J=8.0]; 7.30 - 7.46 [5H, m, aromatics of Bn].

3-[3-(Benzyloxy)phenyl]-2,2-dimethylpropanal 31. A solution of $(COCl)_2$ (125 µl, 1.43 mmol) in dry CH_2Cl_2 (8 ml) was cooled to -78°C and treated with a 1.41 M solution of DMSO in dry CH_2Cl_2 (2.03 ml, 2.86 mmol). After 10 min, a solution of alcohol **30** (155 mg, 572 µmol) in CH_2Cl_2 (2.5 ml) was added. After 15 min triethylamine (415 µl, 2.97 mmol) was introduced, and the mixture allowed to rise to -30°C. The reaction was quenched with saturated aqueous NH_4Cl (5 ml) and extracted with Et_2O. The organic extracts were evaporated to dryness to give crude **31** (single spot in tlc) as a colourless oil, used as such for the next reaction. R_f 0.37 (PE : Et_2O 9:1).

2-[3-(Benzyloxy)phenyl]-2,2-dimethyl-propylidene]-1,3-dithiane 32. A solution of 2-trimethylsilyl-1,3-dithiane (111 µl, 567 µmol) in dry THF (2 ml), cooled to 0°C and maintained under a helium atmosphere, was treated with an 1.6 M solution of *n*-Buli (354 µl, 567 µmol) in hexane. After 15 min a solution of **31** (152 mg, from 567 µmol of **30**) in THF (2 ml) was added and the temperature was allowed to rise to r.t.. After 1.5 hrs an analogous portion of the anion of 2-trimethylsilyl-1,3-dithiane, prepared as above, was added and the reaction was stirred for additional 15 min. The mixture was diluted with brine and extracted with Et_2O. The crude product was chromatographed (PE : Et_2O 100:0 → 98:2) to give pure **32** (171 mg, 81% from **30**) as a pale yellow oil. R_f 0.57 (PE : Et_2O 9:1). ^{1}H n.m.r.: δ 1.16 [6H, s, -C(CH_3)$_2$-]; 2.05 - 2.19 [2H, m, -$SCH_2CH_2CH_2$S-]; 2.81 [2H, s, ArCH_2-]; 2.67 - 2.95 [4H, m, -S$CH_2CH_2CH_2$S-]; 5.07 [2H, s, -OCH_2Ph]; 5.89 [1H, s, -C*H*=C<]; 6.74 - 6.86 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.17 [1H, centre of m, *H* meta to -OBn]; 7.31 - 7.48 [5H, m, aromatics of Bn].

Ethyl 4-[3-(benzyloxy)phenyl]-3,3-dimethylbutanoate 33. Procedure A: a solution of **32** (132 mg, 356 µmol) in EtOH : H_2O 9:1 (35 ml), under a helium atmosphere, was treated with $HgCl_2$ (338 mg, 1.25 mmol) and refluxed for 1 hour. The inorganic salts were filtered off and the mixture diluted with water and CH_2Cl_2. After extraction with CH_2Cl_2 the organic phase was washed with saturated aqueous NH_4Cl and evaporated to dryness. The crude product was chromatographed (PE : Et_2O 97:3 → 85:15) to give two products, **33** (43 mg, 37%) and **35** (20 mg, 20%), both as colourless oils. Procedure B: the procedure is the same as above, but absolute EtOH was used as solvent. After chromatography, compound **33** (92 mg, 79%) was obtained. Compound **33**: R_f 0.52 (PE : Et_2O 85:15). ^{1}H n.m.r.: δ 0.99 [6H, s, -C(CH_3)$_2$]; 1.27 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 2.16 [2H, s, -CH_2CO_2Et]; 2.63 [2H, s, ArCH_2-]; 4.14 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.06 [2H, s, -OCH_2Ph]; 6.76 - 6.88 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.19 [1H, centre of m, *H* meta to -OBn]; 7.31 - 7.48 [5H, m, aromatics of Bn]. Compound **35**: R_f 0.16 (PE : Et_2O 85:15). Anal. found C, 81.60; H, 7.25.

$C_{19}H_{20}O_2$ requires C, 81.40; H, 7.19. ^{1}H n.m.r.: δ 0.99 [6H, s, -C(C*H*$_3$)$_2$]; 2.38 [2H, s, -C*H*$_2$CO-]; 2.73 [2H, s, ArC*H*$_2$-]; 5.04 [2H, s, -OC*H*$_2$Ph]; 6.70 [1H, broad d, *H* ortho to -OBn & -CH$_2$C(CH$_3$)$_2$-, J=2.6]; 6.83 [1H, dd, *H* ortho to -OBn & para to -CH$_2$C(CH$_3$)$_2$-, J =8.8, 2.6]; 7.26 - 7.40 [5H, m, aromatics of Bn]; 7.93 [1H, d, *H* meta to -OBn, J=8.8]. ^{13}C n.m.r.: δ 28.24 [2C, -C(*C*H$_3$)$_2$]; 33.76 [>*C*Me$_2$]; 44.03 [Ar*C*H$_2$CMe$_2$-]; 52.32 [-CMe$_2$*C*H$_2$CO-]; 70.14 [-O*C*H$_2$Ph]; 114.39 & 113.44 [2C, *C*H ortho to -OBn]; 125.74 [-*C*CO-Ar]; 128.22 [Ar*C* para to Bn]; 128.69 & 127.5 [4C, Ar*C* ortho & meta to Bn]; 129.28 [*C*H meta to -OBn]; 136.32 [Ar*C* *ipso* of Bn]; 145.20 [*C*-CH$_2$CMe$_2$ of Ar]; 163.08 [*C*OBn to Ar]; 197.09 [>*C*=O].

Ethyl 4-(3-hydroxyphenyl)-3,3-dimethylbutanoate 34. A solution of **33** (347 mg, 1.06 mmol) in EtSH (5 ml) was treated, at 0°C, with BF$_3$·Et$_2$O (1.04 ml, 8.48 mmol) and stirred at r.t. for 2 hrs. The solution was diluted with water and extracted with Et$_2$O. The combined organic phases were neutralized with 5% aqueous NaHCO$_3$ and solvent was removed. Chromatography (PE : Et$_2$O 8:2 → 7:3) gave pure **34** (177 mg, 71%). R_f 0.20 (PE : Et$_2$O 8:2). Anal. found C, 71.35; H, 8.30. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53. ^{1}H n.m.r.: δ 1.01 [6H, s, -C(C*H*$_3$)$_2$]; 1.28 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.2]; 2.19 [2H, s, -C*H*$_2$CO$_2$Et]; 2.61 [2H, s, ArC*H*$_2$-]; 4.15 [2H, q, -CO$_2$C*H*$_2$CH$_3$, J=7.2]; 4.99 [1H, broad s, -O*H*]; 6.66 - 6.78 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.14 [1H, m, *H* meta to -OBn].

Methoxymethyl [3-[(methoxy)methoxy]phenyl]acetate 36. Methoxymethyl chloride (3 x 4.17 ml, 164.95 mmol) and triethylamine (3 x 7.67 ml, 165.00 mmol) were added portionwise to a solution of 3-hydroxyphenylacetic acid **13** (5.02 g, 32.99 mmol) in dry CH$_3$CN (40 ml) and the resulting mixture was refluxed overnight. Water and saturated aqueous NaHCO$_3$ solution were added and the reaction was extracted with Et$_2$O. The extracts were concentrated in vacuo to give crude **36** (7.52 g), used as such for the next reaction. R_f 0.70 (PE : Et$_2$O 4:6). ^{1}H n.m.r.: δ 3.42 [3H, s, -CO$_2$CH$_2$OC*H*$_3$]; 3.48 [3H, s, ArOCH$_2$OC*H*$_3$]; 3.65 [2H, s, ArC*H*$_2$CO$_2$MOM]; 5.18 [2H, s, ArOC*H*$_2$OCH$_3$]; 5.25 [2H, s, -CO$_2$C*H*$_2$OCH$_3$]; 6.92 - 7.02 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.25 [1H, broad t, *H* meta to -OMOM, J=8.5].

[3-[(Methoxy)methoxy]phenyl]acetic acid 37. It was prepared by the same procedure reported for compound **24**, starting from crude **36** (7.52 g). After extraction and solvent removal crude **37** (5.71 g) was obtained and used in the next reaction, without further purification. ^{1}H n.m.r.: δ 3.48 [3H, s, -OCH$_2$OC*H*$_3$]; 3.63 [2H, s, ArC*H*$_2$CO$_2$H]; 5.18 [2H, s, -OC*H*$_2$OCH$_3$]; 6.90 - 7.00 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.22-7.30 [1H, m, *H* meta to -OMOM]; 8.03 [1H, s, -CO$_2$*H*].

Ethyl 4-[3-[(methoxy)methoxy]phenyl]-3-oxobutanoate 38. Magnesium enolate of malonic acid monoethylester: Magnesium turnings (875 mg, 35.99 mmol) were placed into a two necked flask, equipped with a dropping funnel, and treated with absolute ethanol (1 ml, dried over 3 Å molecular sieves), CCl$_4$ (40 μl) and 1 crystal of iodine. As soon as the pale violet colour of iodine disappeared and the reaction started, the flask was sonicated until complete dissolution of magnesium. During this operation a solution of malonic acid monoethyl ester (prepared following ref. 22a, 4.75 g, 35.97 mmol) in absolute EtOH (3 ml) was slowly added through the dropping funnel. After the addition was complete the reaction flask was warmed to 55°C into the ultrasound bath. About 1 hour later the mixture became very thick and then 4 portions of dry THF, (9 ml, each) were added every 30 min. After all magnesium had dissolved, the solvent was removed under reduced pressure, warming the flask to 80°C. All the EtOH was removed azeotropically by addition of two portion of dry benzene (10 ml each). Finally the white solid obtained was suspended into dry THF (20 ml) and directly used in the homologation reaction. Reaction: crude acid **37** (5.71 g) was dissolved in dry CH$_3$CN (30 ml) and treated with carbonyl diimidazole (5.93 g, 35.83 mmol); after stirring at r.t. for 30 min the colourless solution was transferred into a dropping funnel and slowly added to the magnesium enolate previously prepared. At the end of the addition a solution was obtained; after stirring 30 min at r.t. the flask was warmed at 60°C overnight. The solution was concentrated *in vacuo*, diluted with saturated NH$_4$Cl and the pH adjusted to 7 with 1 N HCl; extraction with EtOAc gave crude **38**. Chromatography (PE : Et$_2$O 9:1 → 8:2) gave pure **38** (4.72 g, 54% from **13**) as a colourless oil. R_f 0.46 (PE : Et$_2$O 1:1). Anal. found C, 63.35; H, 6.70. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81. ^{1}H n.m.r.: δ 1.27 [3H, t, -CO$_2$CH$_2$C*H*$_3$, J=7.2]; 3.46 [2H, s, -COC*H*$_2$CO$_2$Et]; 3.48

[3H, s, -$CO_2CH_2OCH_3$]; 3.80 [2H, s, ArCH_2CO_2Et]; 4.18 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.17 [2H, s, -OCH_2OCH_3]; 6.82 - 7.01 [3H, m, *H* para & 2*H* ortho to -OMOM]; 7.27 [1H, t, *H* meta to -OMOM, J=7.8].

Ethyl 3,3-ethylenedithio-4-(3-hydroxyphenyl)butanoate 39. A solution of **38** (720 mg, 2.70 mmol) in dry CH_2Cl_2 (20 ml) was treated with ethanedithiol (688 µl, 8.20 mmol) and BF_3·Et_2O (1.01 ml, 8.20 mmol). After stirring for 1 hour at r.t. the reaction was diluted with Et_2O, neutralized with saturated aqueous $NaHCO_3$ and extracted again with Et_2O. The solvent was removed under reduced pressure and chromatographed (PE : Et_2O 8:2 → 1:1) to give pure **39** (646 mg, 80%) as a colourless oil. R_f 0.61 (PE : Et_2O 4:6). Anal. found C, 56.15; H, 6.25. $C_{14}H_{18}O_3S_2$ requires C, 56.35; H, 6.08. ^{1}H n.m.r.: δ 1.30 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 2.95 [2H, s, -CH_2CO_2Et]; 3.23 [4H, centre of m, -$S(CH_2)_2S$-]; 3.45 [2H, s, ArCH_2-]; 4.21 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.04 [1H, s, -*OH*]; 6.75 [1H, ddd, *H* ortho to -OH & para to the side chain, J=7.8, 2.6, 0.9]; 6.88 - 6.98 [2H, m, *H* para to -OH & *H* ortho to both substituents]; 7.16 [1H, t, *H* meta to -OH, J=7.8].

Ethyl 4-(3-hydroxyphenyl)-3,3-(propylenedithio)butanoate 40. It was prepared by the same procedure reported for compound **39**, starting from **38**. Chromatography (PE : Et_2O 8:2 → 1:1) gave pure **40** (76%) as a colourless oil. R_f 0.41 (PE : Et_2O 1:1). Anal. found C, 57.55; H, 6.20. $C_{15}H_{20}O_3S_2$ requires C, 57.66; H, 6.45. ^{1}H n.m.r.: δ 1.33 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 1.81 - 2.18 [2H, m, -$SCH_2CH_2CH_2S$-]; 3.00 [2H, s, -CH_2CO_2Et]; 2.67 - 3.12 [4H, m, -$SCH_2CH_2CH_2S$-]; 3.37 [2H, s, ArCH_2-]; 4.23 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.83 [1H, broad s, -*OH*]; 6.77 [1H, ddd, *H* ortho to -OH & para to the side chain, J=7.8, 2.8, 1.1]; 6.98 - 7.08 [2H, m, *H* para to -OH & *H* ortho to both substituents]; 7.19 [1H, t, *H* meta to -OH, J=7.8].

Ethyl 3,3-ethylenedioxy-4-(3-hydroxyphenyl)butanoate 41. Deprotection of phenol: a solution of **38** (1.97 g, 7.40 mmol) in dry CH_2Cl_2, (30 ml) was treated with ethanedithiol (630 µl, 7.51 mmol) and BF_3·Et_2O (940 µl, 7.64 mmol). After 5 min the reaction was worked-up, without tlc control, as described above for compound **39**. Chromatography (PE : Et_2O 7:3 → 45:55) gave deprotected β-ketoester (1.48 g, 90%), which was directly submitted to ketalization. Protection of the carbonyl group: deprotected **38** (1.48 g, 6.66 mmol) was dissolved in 48 ml of dry benzene and treated with ethylene glycol (1.86 ml, 33.30 mmol) and *p*-TSA (628 mg, 3.30 mmol); the resulting solution was refluxed for 24 hrs with azeotropic water remotion. To allow the completeness of the reaction camphorsulfonic acid (78 mg, 336 µmol) was added and the reaction refluxed for 5 hrs more. The mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. Chromatography (PE : EtOAc 65:35 → 1:1) gave pure **41** (1.06 g, 60%) as a colourless oil. R_f 0.32 (PE : EtOAc 1:1). Anal. found C, 63.35; H, 6.60. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81. ^{1}H n.m.r.: δ 1.28 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 2.63 [2H, s, -CH_2CO_2Et]; 3.07 [2H, s, ArCH_2-]; 3.73-3.98 [4H, m, -$O(CH_2)_2O$-]; 4.18 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.88 [1H, s, -*OH*]; 6.72 [1H, ddd, *H* ortho to -OH & para to the side chain, J=8.1, 2.7, 1.0]; 6.82 [1H, t, *H* ortho to both substituents, J=1.4]; 6.88 [1H, dd, *H* para to -OH, J=7.7, 1.1]; 7.15 [1H, t, *H* meta to -OH, J=7.8].

1-[3-(Benzyloxy)phenyl]butan-2-one 42. A solution of **25** (978 mg, 3.43 mmol) in anhydrous THF (20 ml) was cooled to -78°C and treated with EtMgBr (3.43 ml of a 3 M solution in Et_2O, 10.28 mmol). The reaction was allowed to rise to 0°C and then it was quenched with saturated aqueous NH_4Cl solution. Extraction with Et_2O and solvent removal *in vacuo* gave crude **42**. Chromatography (PE : Et_2O 9:1 → 8:2) gave pure **42** as a colourless oil (750 mg, 86%). R_f 0.72 (PE : Et_2O 1:1). Anal. found C, 80.05; H, 7.25 $C_{17}H_{18}O_2$ requires C, 80.28; H, 7.13 ^{1}H n.m.r.: δ 1.02 [3H, t, -$COCH_2CH_3$, J=7.3]; 2.46 [2H, q, -$COCH_2CH_3$, J=7.3]; 3.65 [2H, s, ArCH_2CO-]; 5.06 [2H, s, -OCH_2Ph]; 6.79 - 6.92 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.24 [1H, t, *H* meta to -OBn]; 7.32 - 7.48 [5H, m, aromatics of Bn].

Ethyl 4-[3-(benzyloxy)phenyl]-3-ethyl-3-hydroxybutanoate 43. Anhydrous ethyl acetate (dried over 4Å molecular sieves, 1.00 ml, 10.27 mmol) was added to a 0.25 M solution of LDA (41.8 ml, 10.27 mmol) in THF : *n*-hexane 75 : 25, previously cooled to -78°C. After 10 min ketone **42** (653 mg, 2.57 mmol) in 12 ml of dry THF was added and the resulting solution stirred at the same temperature for 1 hr. The reaction was

quenched with saturated aqueous NH_4Cl solution. Extraction with Et_2O and solvent removal *in vacuo* gave crude **43**. Chromatography (PE : Et_2O 9:1 → 1:1) gave almost pure **43** as a pale yellow oil (871 mg, 99%). R_f 0.39 (PE : Et_2O 7:3). ^1H n.m.r.: δ 0.96 [3H, t, >C(OH)CH_2CH_3, J=8.1]; 1.27 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 1.54 [2H, q, >C(OH)CH_2CH_3, J=7.4]; 2.38 & 2.42 [2H, AB system, CH_2CO_2Et, J=15.7]; 2.80 & 2.81 [2H, AB system, ArCH_2-, J=13.8]; 3.57 [1H, s, -OH]; 4.15 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 5.06 [2H, s, -OCH_2Ph]; 6.81 - 6.88 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.16 - 7.47 [6H, m, aromatics of Bn & *H* meta to -OBn].

Ethyl 4-[3-(benzyloxy)phenyl]-3-ethyl-3-[(triethylsilyl)oxy]butanoate 44. A solution of **43** (511 mg, 1.49 mmol) in dry CH_2Cl_2 (15 ml) was cooled in an ice-bath and treated with 2,6-lutidine (782 μl, 6.71 mmol) and triethylsilyl triflate (1.01 ml, 4.48 mmol). After 1.5 hrs the reaction was diluted with Et_2O and the pH was adjusted to 1 with 1 N HCl; the mixture was extracted with Et_2O and washed until neutral with saturated $NaHCO_3$ solution. After solvent removal crude **44** was chromatographed (PE : Et_2O 95:5 → 8:2) to give pure product as a colourless oil (635 mg, 93%). R_f 0.82 (PE : Et_2O 7:3). Anal. found C, 71.25; H, 8.70 $C_{27}H_{40}O_4Si$ requires C, 71.01; H, 8.83 ^1H n.m.r.: δ 0.56 [6H, q, -Si(CH_2CH_3)$_3$, J=7.9]; 0.90 [9H, t, -Si(CH_2CH_3)$_3$, J=7.4]; 0.95 [3H, t, >C(OTES)CH_2CH_3, J=7.4]; 1.28 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 1.60 [2H, q, >C(OTES)CH_2CH_3, J=7.7]; 2.34 & 2.44 [2H, AB system, CH_2CO_2Et, J=13.7]; 2.90 & 3.02 [2H, AB system, ArCH_2-, J=13.1]; 4.13 [2H, q, -$CO_2CH_2CH_3$, J=7.2]; 5.06 [2H, s, -OCH_2Ph]; 6.79 - 6.97 [3H, m, *H* para & 2*H* ortho to -OBn]; 7.17 [1H, t, *H* meta to -OBn, J=7.8]; 7.27 - 7.46 [5H, m, aromatics of Bn].

Ethyl 3-ethyl-4-(3-hydroxyphenyl)-3-[(triethylsilyl)oxy]butanoate 45 A solution of **44** (631 mg, 1.38 mmol) in 96% ethanol (20 ml) was treated with 10% Pd over charcoal (67 mg) and hydrogenated overnight. The catalyst was filtered off and the solution concentrated *in vacuo*. Chromatography (PE : Et_2O 8:2 → 6:4) gave pure **45** as a colourless oil (480 mg, 95%). R_f 0.60 (PE : Et_2O 6:4). Anal. found C, 65.70; H, 9.55 $C_{20}H_{34}O_4Si$ requires C, 65.53; H, 9.35 ^1H n.m.r.: δ 0.56 [6H, q, -Si(CH_2CH_3)$_3$, J=8.1]; 0.90 [9H, t, -Si(CH_2CH_3)$_3$, J=7.4]; 0.96 [3H, t, >C(OTES)CH_2CH_3, J=7.3]; 1.28 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 1.62 [2H, q, >C(OTES)CH_2CH_3, J=7.0]; 2.37 & 2.46 [2H, AB system, CH_2CO_2Et, J=13.8]; 2.88 & 3.00 [2H, AB system, ArCH_2-, J=13.1]; 4.14 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.67 [1H, s, -OH]; 6.68 [1H, ddd, *H* ortho to -OH & para to the side chain, J=8.1, 2.7, 1.0]; 6.80 [1H, centre of m, *H* ortho to both substituents]; 6.86 [1H, broad d, *H* para to -OH, J=7.7]; 7.12 [1H, t, *H* meta to -OH, J=7.8]. ^{13}C n.m.r.: δ 6.88 [3C, -Si(CH_2CH_3)$_3$]; 7.12 [3C, -Si(CH_2CH_3)$_3$]; 8.35 [>C(OTES)CH_2CH_3]; 14.20 [-OCH_2CH_3]; 32.85 [>C(OTES)CH_2CH_3]; 43.54 & 44.56 [2C, ArCH_2- & CH_2CO_2Et]; 60.31 [-OCH_2CH_3]; 77.35 [>*C*(OTES)CH_2CH_3]; 113.08 & 117.95 [2C, *C* ortho to -OH]; 123.49 [*C* para to -OH]; 128.82 [*C* meta to both the substituents]; 139.80 [≡*C*CH_2C(OTES)<]; 155.10 [≡*C*-OH]; 171.44 [CO_2Et].

Ethyl 3-ethyl-3-hydroxy-4-[3-(hydroxy)phenyl]butanoate 46. It was prepared by the same procedure reported for compound **45**, starting from **43**. Chromatography (PE : Et_2O 1:1 → 3:7) gave pure **46** (90%). R_f 0.33 (PE : Et_2O 1:1). Anal. found C, 66.85; H, 7.80 $C_{14}H_{20}O_4$ requires C, 66.65 H, 7.99 ^1H n.m.r.: δ 0.98 [3H, t, >C(OH)CH_2CH_3, J=7.4]; 1.27 [3H, t, -$CO_2CH_2CH_3$, J=7.2]; 1.56 [2H, q, >C(OH)CH_2CH_3, J=7.4]; 2.40 & 2.44 [2H, AB system, CH_2CO_2Et, J=15.7]; 2.78 & 2.80 [2H, AB system, ArCH_2-, J=13.6]; 3.63 [1H, s, RO*H*]; 4.14 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 4.85 [1H, s, ArO*H*]; 6.68-6.80 [3H, m, *H* para & 2*H* ortho to -OH]; 7.16 [1H, t, *H* meta to -OH, J=7.7].

4-[3-(*t*-Butyldimethylsilyl)oxy]-3,3-(ethylendithio)butanal 47. A solution of **39** (208 mg, 0.7 mmol) in dry DMF (3 ml) was treated with imidazole (90 mg, 1.32 mmol) and *t*-butyldimethylsilyl chloride (143 mg, 0.92 mmol). After stirring for 3 hrs at r.t., the solution was diluted with water and extracted with Et_2O; the combined organic phases were washed twice with water and, finally, with brine. After solvent removal, chromatography (PE : Et_2O 9:1) gave ethyl 4-[3-(t-butyldimethylsilyl)oxy]-3,3-(ethylendithio)butanoate (249 mg, 87%) as a colourless oil. ^1H n.m.r.: δ 0.19 [6H, s, -Si(CH_3)$_2$]; 0.98 [9H, s, *t*-Bu]; 1.30 [3H, t, -$CO_2CH_2CH_3$, J=7.1]; 2.94 [2H, s, -CH_2CO_2Et]; 3.15-3.28 [4H, m, -S(CH_2)$_2$S-]; 3.44 [2H, s, ArCH_2-]; 4.20 [2H, q, -$CO_2CH_2CH_3$, J=7.1]; 6.74 [1H, ddd, *H* ortho to -OSi- & para to the side chain, J=8.0, 2.5, 1.1]; 6.88 [1H, t, *H* ortho to both the substituents, J = 2.0]; 6.95 [1H, dt, *H* para to -OSi-, J=7.8 (d), 1.3 (t)]; 7.14 (1H, t,

H meta to -OSi-, J=7.7]. For the reduction of the ester function to the alcohol see the procedure reported for compound **30**. Chromatography (PE : Et_2O 6:4) gave pure 4-[3-(t-butyldimethylsilyl)oxy]-3,3-(ethylendithio)-1-butanol as a colourless oil (89%). R_f 0.31 (PE : EtOAc 6:4). ^1H n.m.r.: δ 0.19 [6H, s, -Si(CH_3)$_2$]; 0.98 [9H, s, *t*-Bu]; 2.15 [2H, t, CH_2CH_2OH, J = 5.7]; 2.64 [1H, broad s, -O*H*]; 3.02-3.31 [6H, m, -S(CH_2)$_2$S- + ArCH_2-]; 3.95 [2H, t, CH_2OH, J=5.7]; 6.76 [1H, ddd, *H* ortho to -OSi- & para to the side chain, J=8.0, 2.4, 1.1]; 6.89 [1H, t, *H* ortho to both the substituents, J = 2.0]; 6.96 [1H, dt, *H* para to -OSi-, J=7.7 (d), 1.3 (t)]; 7.14 [1H, t, *H* meta to -OSi-, J=7.8]. Swern oxidation of the above described alcohol is the same reported for compound **31**. Crude aldehyde **47** was directly used for the next reaction.

3,3-Ethylenedithio-1,6-dihydroxy-1,2,3,4-tetrahydronaphthalene 48. Crude aldehyde **47** (from 220 μmol of alcohol) was dissolved in dry methanol (3 ml) and cooled to 0°C. A solution of 1 N NaOH in MeOH was added and the resulting solution was allowed to gradually warm to r.t. over a period of 1.5 hrs. Aqueous saturated NH_4Cl solution (10 ml) was added and the mixture extracted with EtOAc. The organic extract was concentrated and directly chromatographed (PE : acetone : MeOH 70:35:5 → 50:50:10) to give **48** (44 mg, 79% from alcohol) as a white solid, nearly insoluble in most common organic solvents. R_f 0.38 (PE : acetone : MeOH 70:35:50.). Anal. found C, 56.40; H, 5.75. $C_{12}H_{14}O_2S_2$ requires C, 56.66; H, 5.55. ^1H n.m.r. (DMSO-d_6; t. = 35°C): δ 2.12 [1H, dd, H_2, J=12.5, 9.5]; 2.50 [1H, centre of m, $H_{2'}$]; 3.04-3.39 [6H, m, H_4 & -S(CH_2)$_2$S-]; 4.65 [1H, centre of m, H_1, J = 7.6, det. through double resonance experiment]; 5.22 [1H, d, RO*H*, J=6.7]; 6.41 [1H, d, H_5, J = 2.2]; 6.62 [1H, dd, H_7, J=8.7, 2.5]; 7.27 [1H, d, H_8, J=8.4]; 9.20 [1H, s, ArO*H*].

General procedure for the cyclization reaction. The ester was dried overnight under vacuo in the presence of P_2O_5, before using it for the reaction. A solution of ester (300 μmol) in dry CH_2Cl_2 (3 ml) was cooled to -78°C and treated with DIBALH (0.66 mmol, 0.66 ml of a 1 M solution in CH_2Cl_2). After 15 min the reaction was quenched with saturated aqueous NH_4Cl (5 ml), warmed to r.t. and stirred for 6 hrs. Then Rochelle's salt (7-8 ml) and Et_2O (7-8 ml) were added and the mixture was stirred until complete separation of the two phases (in some cases filtration through a celite pad was necessary to remove emulsions). After extraction with Et_2O and solvent removal crude product has been used as such for the preparation of the corresponding diacetate or acetonide. Otherwise, for complete characterisation of the 1,8-dihydroxytetralin obtained, chromatography over silica gel plates (PE : Et_2O 7:3) furnished analytical samples; products obtained can be either colourless oils or white solids.

1,8-Dihydroxy-1,2,3,4-tetrahydronaphthalene 53. Yield: 10% (13% based on not recovered **18**). R_f 0.59 (PE : Et_2O 3:7). ^1H n.m.r. : δ 1.70–1.94 [2H, m, H_3]; 2.16-2.30 [2H, m, H_2]; 2.61-2.80 [2H, m, H_4]; 5.06 [1H, broad q, H_1, ΣJ=14.4 determined after treatment with D_2O]; 6.66 [1H, broad d, H_7, J=7.7]; 6.73 [1H, broad d, H_5, J=8.0]; 7.10 [1H, t, H_6, J=7.7]; 7.73 [1H, s, ArO*H*].

4,5-Dihydroxy-benzo[c][2H]dihydropyran 54. Yield: 8%. R_f 0.38 (PE : Et_2O 2:8). ^1H n.m.r. : δ 2.83 [1H, broad s, RO*H*], 3.96 & 4.06 [2H, AB part of ABX system, ArCH(OH)CH_2-, J_{AB}= 12.2, J_{AX} & J_{BX}=4.0, 3.7]; 4.60 & 4.69 [2H, AB system, ArCH_2O-, J=15.0]; 4.82 [1H, dt, ArC*H*(OH)-, ΣJ=7.3]; 6.60 [1H, d, *H* ortho to -OH, J=7.8]; 6.80 [1H, d, *H* para to -OH, J=7.9]; 7.17 [1H, t, *H* meta to -OH, J=7.9]. ^{13}C n.m.r. δ 62.97 [Ar*C*H(OH)-]; 68.18 & 71.65 [2C, ArCH(OH)CH_2- & ArCH_2O-]; 114.62 & 116.15 [2C, *C*H para & *C*H ortho to -OH]; 120.66 [*C* ortho to -OH]; 129.31 [*C*H meta to -OH]; 136.16 [*C* meta to -OH]; 155.84 [≡*C*-OH].

1,8-Dihydroxy-3-methyl-1,2,3,4-tetrahydronaphthalene 55. Yield: not determined; only one diastereoisomer (1,3-cis) of **55** has been isolated as a mixture 18 : 82 (mol/mol) with the starting ester **28**. R_f 0.37 (PE : Et_2O 6:4). ^1H n.m.r. (only selected signals reported): δ 1.08 [3H, d, -CH_3, J= 6.5]; 1.44 [1H, centre of m, H_2], 2.10-2.63 [2H, m, $H_{2'}$ + H_4]; 2.75 [1H, ddd, $H_{4'}$, J=16.2, 4.5, 2.2]; 5.14 [1H, dd, H_1, J=10.6, 5.9]; 6.61-7.18 [3H, m, aromatics].

1,8-Dihydroxy-3,3-dimethyl-1,2,3,4-tetrahydronaphthalene 56. Yield: 65% (69% based on not recovered **34**). R_f 0.47 (PE : Et_2O 7:3). ^1H n.m.r.: δ 0.91 [3H, s, -CH_3(ax)]; 1.07 [3H, s, -CH_3 (eq)]; 1.57 [1H, dd, H_2, J=12.5, 9.8]; 2.03 [1H, ddd, $H_{2'}$, J=12.5, 6.5, 2.2]; 2.43 [1H, broad s, RO*H*]; 2.44 & 2.62 [2H, AB part of

ABX system, H_4, J_{AB}=17.0, J_{AX} & J_{BX}=2.2, 0]; 5.06 [1H, dd, H_1, J=9.5, 6.6]; 6.61 [1H, d, H_7, J=7.9]; 6.71 [1H, broad d, H_5, J=7.9]; 7.09 [1H, t, H_6, J=7.9]; 8.13 [1H, broad s, ArO*H*]. ^{13}C n.m.r.: δ 25.27 [-CH_3 (ax)]; 30.96 [-CH_3 (eq)]; 31.35 [C_3]; 43.57 & 46.05 [2C, C_2 & C_4]; 68.25 [C_1]; 113.99 [C_7]; 120.90 [C_5]; 122.11 [C_{8a}]; 128.99 [C_6]; 137.60 [C_{4a}]; 156.64 [C_8].

3,3-Ethylenedithio-1,8-dihydroxy-1,2,3,4-tetrahydronaphthalene 50. Yield: 42% (49% based on not recovered **39**). R_f 0.51 (PE : Et_2O 6:4). ^{1}H n.m.r. : δ 2.60 & 2.67 [2H, AB part of ABX system, H_2, J_{AB}= 13.6, J_{AX} & J_{BX}=6.4, 4.3]; 3.32-3.45 [6H, m, H_4 + -SCH_2CH_2S-]; 5.06 [1H, dt, H_1, J=10.2, 4.6 ($J_{1,2}$+$J_{1,2'}$)]; 6.68 [1H, dd, H_7, J=7.7, 0.9]; 6.83 [1H, broad d, H_5, J=7.7]; 7.14 [1H, t, H_6, J=7.7]; 7.52 [1H, s, ArO*H*].

1,8-Dihydroxy-3,3-propylenedithio-1,2,3,4-tetrahydronaphthalene 57. Yield: 32%. R_f 0.27 (PE : Et_2O 1:1). ^{1}H n.m.r. : δ 1.81–2.28 [2H, m, -S$CH_2CH_2CH_2$S-]; 2.50 [1H, dd, H_2, J=14.6, 6.1]; 2.71-2.83 [2H, m, -SCH_2-]; 2.98 [1H, ddd, $H_{2'}$, J=14.6, 3.4, 1.8]; 3.02-3.25 [4H, m, H_4 + -SCH_2-]; 3.61 [1H, d, -O*H*, J=11.1]; 4.99 [1H, ddd, H_1, J=11.1, 6.1, 3.4]; 6.69 [1H, broad d, H_7, J=7.9]; 6.84 [1H, broad d, H_5, J=7.9]; 7.18 [1H, t, H_6, J=7.9]; 7.23 [1H, s, ArO*H*].

3,3-Ethylenedioxy-1,8-dihydroxy-1,2,3,4-tetrahydronaphthalene 58. Yield: 47% (52% based on not recovered **41**). R_f 0.31 (PE : Et_2O 25:75). ^{1}H n.m.r. : δ 2.14–2.34 [2H, m, H_2]; 2.96 [2H, s, H_4]; 3.27 [2H, broad d, RO*H* , J=7.9]; 3.94-4.11 [4H, m, -OCH_2CH_2O-]; 5.10 [1H, broad s, H_1, became t after treatment with D_2O, J=4.9]; 6.67 [1H, dd, H_7, J=7.6, 0.7]; 6.79 [1H, d, H_5, J=7.7]; 7.12 [1H, broad s, ArO*H*]; 7.15 [1H, t, H_6, J=7.8].

3-Ethyl-1,8-dihydroxy-3-[(triethylsilyl)oxy]-1,2,3,4-tetrahydronaphthalene 59. Yield: 56% (64% based on not recovered **45**) Diastereomeric ratio: 77 : 23 (determined by ^{1}H-n.m.r.). R_f 0.60 (diastereoisomer A), 0.54 (diastereoisomer B) (PE : Et_2O 6:4). ^{1}H n.m.r. : Diastereoisomer A [isolated as a 77 : 23 (w/w) mixture with starting ester **45**] δ 0.48 [6H, centre of m , -Si(CH_2CH_3)$_3$]; 0.77 [9H, t, -Si(CH_2CH_3)$_3$, J=7.3]; 0.99 [3H, t, -CH_2CH_3, J=7.4]; 1.50-1.8 [2H, m, -CH_2CH_3]; 1.93 [1H, dd, H_2, J=14.2, 5.9]; 2.23 [1H, dt, $H_{2'}$, J=14.3, 2.4]; 2.72 & 2.84 [2H, AB part of ABX system, H_4, J_{AB}=17.6, J_{AX} & J_{BX}=2.5, ≅ 0]; 3.50-3.58 [1H, m, RO*H*]; 4.89 [1H, broad s, H_1, became dd after treatment with D_2O, J=5.8, 2.1]; 6.65 [1H, d, H_7, J=7.7]; 6.80 [1H, d, H_5, J=8.0]; 7.04 [1H, broad s, ArO*H*]; 7.14 [1H, t, H_6, J=7.8]. Diastereoisomer B δ 0.44 [6H, centre of m , -Si(CH_2CH_3)$_3$]; 0.77 [9H, t, -Si(CH_2CH_3)$_3$, J=7.18]; 0.93 [3H, t, -CH_2CH_3, J=7.4]; 1.52-1.75 [3H, m, -CH_2CH_3 + H_2]; 2.12 [1H, broad s, RO*H*]; 2.35 [1H, ddd, $H_{2'}$, J=12.3, 6.2, 2.6]; 2.65 [1H, dd, H_4, J=16.9, 2.6]; 2.92 [1H, d, H_4, J=16.8]; 5.28 [1H, broad dd, *H*, J=9.6, 6.3]; 6.60 [1H, d, H_7, J=7.6]; 6.72 [1H, d, H_5, J=8.1]; 7.10 [1H, t, H_6, J=7.7]; 8.21 [1H, broad s, ArO*H*]. ^{13}C n.m.r. : Diastereoisomer A δ 6.44 [3C, -Si(CH_2CH_3)$_3$]; 6.75 [3C, -Si(CH_2CH_3)$_3$]; 8.52 [>C(OTES)CH_2CH_3]; 34.96 [>C(OTES)CH_2CH_3]; 40.82 [C_2]; 41.62 [C_4]; 65.68 [C_1]; 75.63 [C_3]; 114.19 [C_7]; 121.08 [C_5]; 123.90 [C_{8a}]; 129.00 [C_6]; 134.63 [C_{4a}]; 156.31 [C_8]. Diastereoisomer B δ 6.52 [3C, -Si(CH_2CH_3)$_3$]; 6.88 [3C, -Si(CH_2CH_3)$_3$]; 8.37 [>C(OTES)CH_2CH_3]; 35.55 [>C(OTES)CH_2CH_3]; 41.56 [C_2]; 43.24 [C_4]; 69.20 [C_1]; 75.70 [C_3]; 114.02 [C_7]; 120.83 [C_5]; 122.65 [C_{8a}]; 128.97 [C_6]; 136.31 [C_{4a}]; 156.42 [C_8].

General procedure for acetylation of the cyclization products. Crude 1,8-dihydroxytetralin (from 300 μmol of ester) was dissolved in dry CH_2Cl_2 (5 ml) and cooled to 0°C. Acetic anhydride (85 μl, 900 μmol), triethylamine (125 μl, 900 μmol) and 4-dimethylaminopyridine (1.8 mg, 15 μmol) were added and the solution stirred at r.t. for 30 min. The mixture was diluted with water and extracted with Et_2O. After solvent removal chromatography over silica gel plates (PE : Et_2O 8:2) furnished the corresponding diacetate.

1,8-Diacetoxy-1,2,3,4-tetrahydronaphthalene 60. Yield: 10% (18% based on not recovered O-acetylated **18**). R_f 0.54 (PE : Et_2O 1:1). ^{1}H n.m.r. [mixture 74:26 (mol/mol) of O-acetylated **18** and **60**]: δ 1.7–3.0 [6H, m, H_2 + H_3 + H_4]; 2.03 [3H, s, CH_3CO_2R]; 2.29 [3H, s, CH_3CO_2Ar]; 6.11 [1H, broad t, H_1, J=6.5]; 6.90-7.33 [3H, m, H_5 + H_6 + H_7]. ^{13}C n.m.r.: δ 17.59 [C_3]; 20.80 & 21.15 [2C, -OCOCH_3]; 28.91 [C_2]; 33.54 [C_4]; 63.97 [C_1]; 120.03 [C_7]; 126.25 [C_{8a}]; 126.90 [C_5]; 128.93 [C_6]; 140.19 [C_{4a}]; 149.79 [C_8]; 169.54 & 170.15 [2C, -O$COCH_3$].

1,8-Diacetoxy-3-methyl-1,2,3,4-tetrahydronaphthalene 61. Yield: 38% (52% based on not recovered O-acetylated **28**) as an approximately 1 : 1 diastereomeric mixture. R_f 0.33 (PE : Et_2O 7:3). ^{1}H n.m.r. [mixture

79:21 (mol/mol) of **61** (both diast.) and O-acetylated **28**]: δ 0.90 [3H, d, CH_3 diast. A, J=6.6]; 1.08 [3H, d, CH_3 diast. B, J=6.6]; 1.4–2.85 [12H, m, H_2 + H_3 + H_4 of both diast.]; 2.29 & 2.23 [6H, 2s, CH_3CO_2Ar of both diast.]; 2.06 & 2.04 [6H, 2s, CH_3CO_2R of both diast.]; 6.17 [2H, broad t, H_1 of both diast., J=7.3]; 6.80-7.33 [6H, m, H_5 + H_6 + H_7 of both diast.]. ^{13}C n.m.r.: δ 19.20 & 19.50 [2C, -CH_3 of both diast.]; 20.90, 20.96 & 21.14, 21.27 [4C, -OCOCH_3 of both diast.]; 31.89 & 32.11 [2C, C_3 of both diast.]; 37.42 & 37.90 [2C,C_2 of both diast.]; 42.67 & 43.21 [2C, C_4 of both diast.]; 62.75 [2C, C_1 of both diast.]; 119.01 & 119.18 [2C, C_7 of both diast.]; 122.14 & 122.22 [2C, C_5 of both diast.]; 126.55 & 126.65 [2C, C_{8a} of both diast.]; 129.07 & 129.11 [2C, C_6 of both diast.]; 142.01 & 142.45 [2C, C_{4a} of both diast.]; 169.40 & 170.40 [4C, -O$COCH_3$ of both diast.].

1,8-Diacetoxy-3,3-dimethyl-1,2,3,4-tetrahydronaphthalene 62. Yield: 60% (64% based on not recovered O-acetylated **34**). Anal. found C, 69.25; H, 7.10. $C_{16}H_{20}O_4$ requires C, 69.55; H, 7.30. R_f 0.25 (PE : Et_2O 8:2). ^1H n.m.r.: δ 0.94 [3H, s, -CH_3 (ax)]; 0.98 [3H, s, -CH_3 (eq)]; 1.97 [3H, s, CH_3CO_2R]; 2.16 [3H, s, CH_3CO_2Ar]; 1.66 [1H, ddd, H_2, J=14.5, 4.2, 1.2]; 1.86 [1H, dd, $H_{2'}$, J=14.5, 5.9]; 2.48 & 2.61 [2H, AB system, H_4, J= 16.3]; 6.05 [1H, dd, H_1, J=5.9, 4.2]; 6.85 [1H, d, H_7, J=8.1]; 6.93 [1H, d, H_5, J=7.7]; 7.19 [1H, t, H_6, J=7.9]. ^{13}C n.m.r.: δ 20.85 & 21.10 [2C, -OCOCH_3]; 27.93 [-CH_3 (ax)], 29.27 [-CH_3 (eq)]; 29.67 [C_3]; 41.88 & 43.51 [2C, C_2 & C_4]; 65.80 [C_1]; 120.33 [C_7]; 125.63 [C_{8a}]; 126.98 [C_5]; 128.95 [C_6]; 139.52 [C_{4a}]; 149.94 [C_8]; 169.15 & 170.24 [2C, -O$COCH_3$].

1,8-Diacetoxy-3,3-ethylenedithio-1,2,3,4-tetrahydronaphthalene 63. Yield: 54% (75% based on not recovered O-acetylated **39**). Anal. found C, 56.50; H, 5.50. $C_{16}H_{18}O_4S_2$ requires C, 56.78; H, 5.36. R_f 0.38 (PE : Et_2O 1:1). ^1H n.m.r.: δ 2.07 [3H, s, CH_3CO_2R]; 2.25 [3H, s, CH_3CO_2Ar]; 2.51 [1H, ddd, H_2, J=14.4, 4.2, 1.3]; 2.76 [1H, dd, $H_{2'}$, J= 14.4, 5.8]; 3.30-3.41 [4H, m, -SCH_2CH_2S-]; 3.28 & 3.49 [2H, AB system, H_4, J=16.6]; 6.22 [1H, dd, H_1, J=5.8, 4.2]; 7.31 [1H, t, H_6, J=7.8]; 7.50 [2H, dd, H_5 & H_7, J=7.8, 1.8]. ^{13}C n.m.r.: δ 20.72 & 20.92 [2C, -OCOCH_3]; 38.94 & 39.19 [2C, -SCH_2CH_2S-]; 43.38 & 46.83 [2C, C_2 & C_4]; 63.04 [C_3]; 65.75 [C_1]; 121.07 [C_7]; 124.75 [C_{8a}]; 126.24 [C_5]; 129.27 [C_6]; 138.68 [C_{4a}]; 149.80 [C_8]; 168.86 & 169.91 [2C, -O$COCH_3$].

1,8-Diacetoxy-3,3-propylenedithio-1,2,3,4-tetrahydronaphthalene 64. Yield: 40% (54% based on not recovered O-acetylated **40**). Anal. found C, 57.95; H, 5.50. $C_{17}H_{20}O_4S_2$ requires C, 57.93; H, 5.72. R_f 0.31 (PE : Et_2O 6:4). ^1H n.m.r.: δ 2.09 [3H, s, CH_3CO_2R]; 2.24 [3H, s, CH_3CO_2Ar]; 1.96-2.10 [2H, m, -S$CH_2CH_2CH_2$S-]; 2.34 [1H, centre of m, H_2]; 2.80–2.95 [5H, m, -S$CH_2CH_2CH_2$S- + $H_{2'}$]; 3.20 & 3.40 [2H, AB system, H_4, J=16.4]; 6.18 [1H, t, H_1, J=5.9]; 7.01 [2H, broad t, H_5 + H_6, J=7.9]; 7.32 [1H, t, H_7, J=7.9].^{13}C n.m.r.: δ 20.81 & 20.99 [2C, -OCOCH_3]; 25.15 [-S$CH_2CH_2CH_2$S-]; 26.38 & 26.42 [2C, -S$CH_2CH_2CH_2$S-]; 40.21 & 42.29 [2C, C_2 & C_4]; 46.71 [C_3]; 65.29 [C_1]; 121.33 [C_7]; 125.15 [C_{8a}]; 126.38 [C_5]; 129.30 [C_6]; 136.26 [C_{4a}]; 149.66 [C_8]; 168.86 & 170.18 [2C, -O$COCH_3$].

1,8-Diacetoxy-3-ethyl-3-[(triethylsilyl)oxy]-1,2,3,4-tetrahydronaphthalene 65. In this case usual acetylation conditions gave low yield of products; this procedure was followed: crude 1,8-dihydroxytetralin (from 300 μmol of ester) was dissolved in dry pyridine (0.5 ml) and treated with acetic anhydride (85 μl, 900 μmol). After 3 hrs the mixture was diluted with water and ether and the pH adjusted to 1 with 1 N HCl. The mixture was rapidly extracted and the combined organic extracts washed until neutral with saturated aqueous $NaHCO_3$. After solvent removal usual purification was followed. Yield: 43% (58% based on not recovered O-acetylated **45**). The isolated product is a 80 : 20 (w/w) mixture of diastereomeric acetates (diastereomeric ratio 77 : 23) and acetylated diol derived from overreduction of starting **45**. R_f 0.52 (PE : Et_2O 7:3). ^1H n.m.r.: Diastereoisomer A δ 0.46-0.59 [12H, m, -Si(CH_2CH_3)$_3$, both diast.]; 0.88 [18H, t, -Si(CH_2CH_3)$_3$, J=7.4, both diast]; 0.91 [6H, t, -CH_2CH_3 both diast., J=7.4]; 1.49 [2H, q, -CH_2CH_3, J=7.4]; 1.94-2.03 [2H, m, H_2]; 2.05 [6H, s, CH_3CO_2R, both diast.]; 2.24 [6H, s, CH_3CO_2Ar, both diast.]; 2.86 & 2.95 [2H, AB system, H_4, J=16.2]; 6.09 [1H, broad t, H_1, J=6.1]; 6.93 [2H, broad d, H_7, J=8.0, both diast.]; 7.00 [2H, broad d, H_5, J=7.3, both diast.]; 7.28 [2H, t, H_6, J=7.8, both diast.]. Diastereoisomer B (see also diast. A) 1.64 [2H, centre of m, -CH_2CH_3]; 2.20 [2H, dd, H_2, J=7.1, 6.2]; 2.81 & 2.99 [2H, AB system, H_4, J=16.1]; 6.22 [1H, dd H_1, J=6.2, 4.5]. ^{13}C n.m.r. : Diastereoisomer A δ 6.73 [3C, -Si(CH_2CH_3)$_3$]; 7.02 [3C, -Si(CH_2CH_3)$_3$]; 7.97 [>C(OTES)CH_2CH_3]; 20.92 & 21.15 [2C, -OCOCH_3]; 33.00 [>C(OTES)CH_2CH_3]; 40.16 [C_2]; 42.40 [C_4];

66.06 [C_1]; 73.41 [C_3]; 120.62 [C_7]; 125.83 [C_{8a}]; 126.92 [C_5]; 129.14 [C_6]; 138.63 [C_{4a}]; 149.73 [C_8]; 169.23 & 170.48 [2C, -OCOCH$_3$]. Diastereoisomer B δ 6.73 [3C, -Si(CH_2CH_3)$_3$]; 7.02 [3C, -Si(CH_2CH_3)$_3$]; 8.09 [>C(OTES)CH_2CH_3]; 20.92 & 21.15 [2C, -OCOCH_3]; 33.22 [>C(OTES)CH_2CH_3]; 439.80 [C_2]; 42.84 [C_4]; 68.79 [C_1]; 74.04 [C_3]; 120.62 [C_7]; 125.59 [C_{8a}]; 126.99 [C_5]; 129.14 [C_6]; 138.82 [C_{4a}]; 149.65 [C_8]; 169.23 & 170.21 [2C, -O$COCH_3$].

General procedure for the preparation of the O,O-isopropylidene derivatives of the cyclization products. Crude 1,8-dihydroxytetralin (from 300 μmol of ester) was dissolved in dry CH_2Cl_2 (5 ml) and cooled to 0°C. 2-Methoxypropene (71 μl, 75 μmol) and 0.01 M solution of *p*-TSA (600 μl, 6 μmol) in dry THF were added. After 15' stirring at 0°C triethylamine (418 μl, 3.0 mmol) was added and the solution concentrated under reduced pressure. Direct chromatography over silica gel plates (PE : Et_2O 95:5) furnished the corresponding isopropylidene derivatives.

1,8-[(Isopropylidene)dioxy]-1,2,3,4-tetrahydronaphthalene 66. Yield: 2%. R_f 0.71 (PE : Et_2O 1:1). ^{1}H n.m.r. (the reaction gave many byproducts and **66** has been isolated in mixture with some of them): δ 1.559 & 1.563 [6H, 2s, (CH_3)$_2$C-]; 1.70-2.90 [4H, m, $H_2 + H_3$]; 3.36 [2H, centre of m, H_4]; 4.80 [1H, dd, H_1, J=11.4, 5.1]; 6.60 [1H, dd, H_7, J=8.0, 0.9]; 6.66 [1H, dd, H_5, J=8.0, 0.9]; 7.01 [1H, t, H_6, J=8.0]. ^{13}C n.m.r.: δ 20.10 [C_3]; 23.62 & 28.67 [2C, (CH_3)$_2$C-]; 28.27 [C_2]; 39.19 [C_4]; 67.05 [C_1]; 100.57 [(CH_3)$_2C$-]; 113.17 [C_7]; 119.78 [C_5]; 120.88 [C_{8a}]; 127.98 [C_6]; 135.93 [C_{4a}]; 150.63 [C_8].

1,8-[(Isopropylidene)dioxy]-3-methyl-1,2,3,4-tetrahydronaphthalene 67. Yield: 8%. R_f 0.89 (PE : Et_2O 7:3). ^{1}H n.m.r. (1,3-cis diastereoisomer): δ 1.10 [3H, d, -CH_3, J=6.5]; 1.58 & 1.59 [6H, 2s, (CH_3)$_2$C-]; 1.36 [1H, centre of m, H_2]; 1.95-2.15 [2H, m, $H_{2'} + H_3$]; 2.38 [1H, dd, H_4 , J=17.1, 11.5]; 2.95 [1H, dd, $H_{4'}$, J=17.1, 5.9]; 4.85 [1H, dd, H_1, 10.7, 3.8]; 6.58-6.67 [2H, m, $H_5 + H_7$]; 7.07 [1H, t, H_6, J=7.1]. ^{13}C n.m.r: δ 22.51 [-$CHCH_3$]; 23.87 & 28.69 [2C, (CH_3)$_2$C-]; 27.59 [C_3]; 36.93 & 37.00 [2C, C_2 & C_4]; 67.26 [C_1]; 100.83 [(CH_3)$_2C$-]; 113.12 [C_7]; 119.70 [C_5]; 120.65 [C_{8a}]; 128.08 [C_6]; 135.86 [C_{4a}]; 150.85 [C_8].

3,3-Dimethyl-1,8-[(isopropylidene)dioxy]-1,2,3,4-tetrahydronaphthalene 68. Yield: 55%. ^{1}H n.m.r.: δ 1.05 [3H, s, -CH_3 (ax)]; 1.10 [3H, s, -CH_3 (eq)]; 1.57 & 1.60 [6H, 2s, (CH_3)$_2$C-]; 1.47 [1H, t, H_2, J=11.6]; 1.93 [1H, dd, $H_{2'}$, J=12.1, 5.8]; 2.55 [2H, s, H_4]; 4.83 [1H, dd, H_1, J=11.3, 5.9]; 6.64 [2H, centre of m, $H_5 + H_7$]; 7.08 [1H, t, H_6, J=7.9]. ^{13}C n.m.r.: 23.86 & 28.15* [2C, (CH_3)$_2$C-]; 28.68* [-CH_3 (ax)], 32.39 [-CH_3 (eq)]; 30.36 [C_3]; 41.76 & 42.33 [2C, C_2 & C_4]; 64.97 [C_1]; 101.09 [(CH_3)$_2C$-]; 113.24 [C_7]; 119.97 [C_5]; 120.58 [C_{8a}]; 128.04 [C_6]; 135.85 [C_{4a}]; 150.76[C_8]. * interchangeable signals.

3,3-Ethylenedithio-1,8-[(isopropylidene)dioxy]-1,2,3,4-tetrahydronaphthalene 69. Yield: 40%. R_f 0.80 (PE : Et_2O 6:4). ^{1}H n.m.r.: δ ^{1}H n.m.r. : δ 1.57 & 1.63 [6H, 2s, (CH_3)$_2$C-]; 2.26 [1H, dd, H_2, J=12.5, 10.8]; 2.66 [1H, dd, $H_{2'}$, J= 12.5, 5.3]; 3.37-3.49 [6H, m, H_4 + -SCH_2CH_2S-]; 5.05 [1H, dd, H_1, J=10.8, 5.3]; 6.65 [2H, broad d, $H_5 + H_7$, J=8.0]; 7.12 [1H, t, H_6, J=8.0]. ^{13}C n.m.r.: δ 24.16 & 28.57 [2C, (CH_3)$_2$C-]; 38.92 & 39.81 [2C, -SCH_2CH_2S-]; 44.32 & 45.55 [2C, C_2 & C_4]; 64.03 [C_3]; 66.31 [C_1]; 101.57 [(CH_3)$_2C$-]; 113.91 [C_7]; 119.38 [C_5]; 119.53 [C_{8a}]; 128.54 [C_6]; 133.98 [C_{4a}]; 151.05 [C_8].

1,8-[(Isopropylidene)dioxy]-3,3-trimethylenedithio-1,2,3,4-tetrahydronaphthalene 70. Yield: 40%. R_f 0.66 (PE : Et_2O 8:2). ^{1}H n.m.r. : δ 1.59 & 1.61 [6H, 2s, (CH_3)$_2$C-]; 1.93-2.19 [2H, m, -S$CH_2C$$H_2CH_2$S-]; 1.97 [1H, dd, H_2, J=12.4, 10.9]; 2.78–3.09 [5H, m, -S$CH_2CH_2C$$H_2$S- + $H_{2'}$]; 3.20 & 3.28 [2H, AB system, H_4, J=16.8]; 5.04 [1H, dd, H_1, J=10.9, 5.4]; 6.69 [2H, centre of m, $H_5 + H_6$]; 7.13 [1H, t, broad H_7, J=7.9].^{13}C n.m.r.: δ 23.77 & 28.51 [2C, (CH_3)$_2$C-]; 25.15 [-$SCH_2CH_2CH_2$S-]; 26.61 & 27.06 [2C, -S$CH_2CH_2CH_2$S-]; 40.10 & 42.17 [2C, C_2 & C_4]; 46.87 [C_3]; 64.46 [C_1]; 101.16 [(CH_3)$_2C$-]; 113.96 [C_7]; 119.47 [C_5]; 119.75 [C_{8a}]; 128.47 [C_6]; 132.50 [C_{4a}]; 150.52 [C_8].

3-Ethyl-1,8-[(isopropylidene)dioxy]-3-[(triethylsilyl)oxy]-1,2,3,4-tetrahydronaphthalene 71. Yield: 40% (as a 77 : 23 diastereomeric mixture). R_f 0.91 (PE : Et_2O 9:1). ^{1}H n.m.r.: Diastereoisomer A δ 0.48-0.61 [12H, m, -Si(CH_2CH_3)$_3$, both diast.]; 0.88 [18H, t, -Si(CH_2CH_3)$_3$, J=7.4, both diast.]; 0.87-1.03 [6H, m, -CH_2CH_3, both diast.]; 1.48-1.87 [5H, m, -CH_2CH_3 & H_2, both diast.]; 1.59 & 1.57 [12H, 2s, (CH_3)$_2$C-, both diast.]; 2.34 [1H, dd, $H_{2'}$, J=11.4, 2.6]; 2.83 & 2.88 [2H, AB system, H_4, J=13.7]; 4.69 [1H, dd, H_1, J=11.4, 5.9]; 6.68-6.59 [4H, m, $H_5 + H_7$, both diast.]; 7.10 [1H, t, H_6, J=7.7]. Diastereoisomer B (see also diast. A) δ

2.19 [1H, ddd, H_2, J=12.1, 5.2, 1.0]; 2.82 & 2.88 [2H, AB system, H_4, J=17.9]; 5.12 [1H, dd, H_1, J=11.4, 5.1]; 7.08 [1H, t, H_6, J=7.9]. ^{13}C n.m.r.: Diastereoisomer A δ 6.72 [3C, -Si(CH_2CH_3)$_3$]; 7.08 [3C, -Si(CH_2CH_3)$_3$]; 7.71 [>C(OTES)CH_2CH_3]; 23.90 & 28.60 [2C, (CH_3)$_2$C-]; 33.88 [>C(OTES)CH_2CH_3]; 40.90 [C_2]; 42.58 [C_4]; 65.31 [C_1]; 74.35 [C_3]; 101.26 [(CH_3)$_2C$-]; 113.40 [C_7]; 119.88 [C_{8a}]; 120.04 [C_5]; 128.36 [C_6]; 134.95 [C_{4a}]; 150.73 [C_8]. Diastereoisomer B δ 6.72 [3C, -Si(CH_2CH_3)$_3$]; 7.08 [3C, -Si(CH_2CH_3)$_3$]; 8.46 [>C(OTES)CH_2CH_3]; 23.65 & 28.68 [2C, (CH_3)$_2$C-]; 36.77 [>C(OTES)CH_2CH_3]; 39.43 [C_2]; 41.06 [C_4]; 65.04 [C_1]; 75.47 [C_3]; 100.90 [(CH_3)$_2C$-]; 113.04 [C_7]; 119.77 [C_5]; 120.25 [C_{8a}]; 128.09 [C_6]; 134.42 [C_{4a}]; 150.36 [C_8].

REFERENCES AND NOTES

1. Part of this work was reported in a preliminary communication (Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1992**, *33*, 3919-3922).
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. **a)** Riva, R.; Banfi, L.; Danieli, B.; Guanti, G.; Lesma, G.; Palmisano, G. *J.Chem. Soc., Chem. Commun.* **1987**, 299-300; **b)** Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4335-4338; **c)** Guanti, G.; Baldaro, E.; Banfi, L.; Guaragna, A.; Narisano, E.; Valcavi, U. *Tetrahedron* **1988**, *44*, 3685-3692; **d)** Guanti, G.; Banfi, L.; Narisano E. *Tetrahedron Lett.* **1989**, *30*, 5507-5510; **e)** Guanti, G.; Banfi, L.; Ghiron, C.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 267-270; **f)** Guanti, G.; Banfi, L.; Narisano, E.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 2221-2222; **g)** Guanti, G.; Banfi, L.; Narisano, E.; Thea, S. *Synlett.* **1992**, 311-312; **h)** Guanti, G.; Banfi, L.; Narisano, E.; Zannetti, T. *J. Org. Chem.* **1993**, *58*, 1508-1514.
4. As far as we know the only example of an intramolecular hydroxyalkylation of phenol derivatives has been reported by Krohn (ref. 2b). However, it concerns anthraquinone derivatives (from aloe-emodin) which are known to cyclize *via* a Marschalk-type reaction.
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9. Wittig-Horner olefination of aldehyde **16** with triethyl phosphonoacetate in heterogeneous medium, in absence of solvent (Villieras, J.; Rambaud, M. *Synthesis* **1983**, 300-303) gave a considerably lower yield (41%) of **17**.
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11. The direct transformation of **20** into **22** was unsuccessfully attempted; treatment of **20** with sodium hydride, followed by addition of ethyl chloroacetate (Ramadas, S. R.; Chaudhuri, A. P. *J. Chem. Soc., Chem. Commun.* **1974**, 521-522) gave a very slow reaction, **22** being obtained only in little amounts; also using chloroacetic acid we did not succeed in the nucleophilic substitution and obtained only unidentified byproducts.
12. The *t*-butyl ester was transformed into the corresponding ethyl ester, due to its inertness to DIBALH, during the cyclization reaction.
13. The transformation of **24** into the corresponding S-pyridyl thioate (Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763-4765) worked also well but the addition of dimethyllithium cuprate gave only moderate yield of ketone **26** (Kim, S.; Lee, J. I. *J. Org. Chem.* **1983**, *48*, 2608-2610), while the corresponding Grignard or lithium reagent led exclusively to the formation of the tertiary alcohol.
14. The preparation of **25** by a shorter route, that is formation of the hydroxamate of acid **13**, followed by

benzylation of the phenolic hydroxy group, gave lower overall yields (66% from **13**).
15. Attempted direct preparation of **25** from **15**, by treatment with the reagent prepared *in situ* from trimethylaluminium and N,O-dimethyl hydroxylamine hydrochloride (Levin, J. I.; Toros, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *19*, 989-993), gave an unusually sluggish reaction and, by forcing the reaction conditions, that is working at 50°C, side reactions took place.
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18. The direct reaction of the acid **24** with MeLi (Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566-1568) gave only little amounts of **26**.
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22. The direct homologation of **29** to give **33**, *via* α-bromo α-keto dianion rearrangement failed (Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429-1430).
23. The transformation of **30** into the corresponding cyanide, derived from nucleophilic substitution of the mesylate of **30** failed, due to the inertness of the latter compound also in the presence of various anionic activators.
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