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Exploitation of Highly Functionalised Epoxides Derived from Asymmetrized *Tris*(hydroxymethyl)methane (THYM*) in the Synthesis of a Fragment of Lasalocide A and Other Related Polyether Ionofore Antibiotics

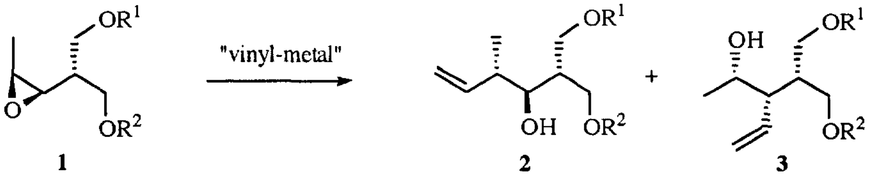
Giuseppe Guanti and Enrica Narisano

Dipartimento di Chimica e Chimica Industriale dell'Università & C.N.R. Centro di Studio per la Chimica dei Composti
Cicloalifatici ed Aromatici, Via Dodecaneso 31, I-16146 Genova (Italy)

Abstract: A fragment for the total convergent synthesis of some polyether ionophore antibiotics (lasalocide A, isolasalocide A, lysocellin) has been obtained through "higher order" vinyl cuprate ring opening of functionalised epoxides derived from THYM*.

In the last few years we have been involved in a research project aimed to the *enantio-* and *diastereodivergent*[1] synthesis of a series of *cis* epoxides[2] derived from asymmetrized *tris* (hydroxymethyl)methane (THYM*)[3] and the subsequent elaboration of these highly functionalised small building blocks through the oxirane ring opening.[4] In particular, we have extensively studied the nucleophilic reaction with organometallic reagents, that allows the regioselective formation of a new C-C bond, although only "simple" (not functionalised) alkyl groups were used.[4b] The use of "functionalised" *C*-nucleophiles would obviously lead to more sophisticated intermediates. Since cyanide-based nucleophilic reagents had shown not completely satisfying results,[4b] we turned our attention to "vinyl-metal" reagents (Scheme 1),[5] with the aim to obtain unsaturated derivatives to be elaborated.

On the base of previous studies,[4] it would be easily predictable that better results would be obtained



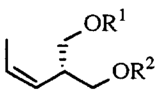
	R^1	R^2		R^1	R^2
a	PMBOM	BOM	**c**	PMBOM	TBDMS
b	TIPS	PMP	**d**	TIPS	H

Scheme 1

Table 1. Ring Opening of Epoxides **1** Using "Vinyl-Metal" Reagents (Scheme 1)

	Subs	R^1, R^2	"Vinyl-metal"[a]	Solvent	Lewis acid[b]	T, °C (t, h)	Yield,[c] %	2 : 3 Ratio[d]
1	**1a**	PMBOM, BOM	$(CH_2{=}CH)_2CuCNLi_2$	Et_2O	$BF_3 \cdot Et_2O$	-78(2) → -10 (20)	84[e]	94 : 6
2	**1b**	TIPS, PMP	$(CH_2{=}CH)_2CuCNLi_2$	Et_2O	$BF_3 \cdot Et_2O$	-78 (2.5)	75[f]	90 : 10
3	**1c**	PMBOM, TBDMS	$(CH_2{=}CH)_2CuCNLi_2$	Et_2O	$BF_3 \cdot Et_2O$	-78 (2.5)	62[g]	87 : 13
4	**1d**	TIPS, H	$(CH_2{=}CH)_2CuCNLi_2$	THF	-	-10 (20) → rt (24) → 70 (1)	-[h]	-
5	**1d**	TIPS, H	$CH_2{=}CHMgBr$	Et_2O	$CuBr \cdot Me_2S$	-20 (24) → rt (5)	-[i]	-

[a] A tenfold excess of reagent was usually employed. [b] A twofold excess of Lewis acid was usually employed. [c] Isolated yields. [d] Products identification rests on ^1H and ^{13}C NMR spectra, with the aid of DEPT, COSY, and HETCOR experiments. Products ratio was usually determined by weighing isolated regioisomers. [e] Alkene **4a** was obtained as a by-product (2%). [f] Alkene **4b** was obtained as a by-product (9%). [g] Alkene **4c** was obtained as a by-product (19%), along with a small amount of **6** (yield not determined). [h] No reaction occurred. [i] Only formation of bromohydrin **5** (4%) was observed.



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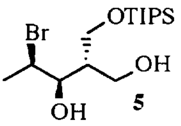

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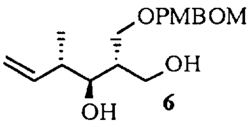

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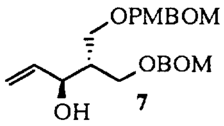

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using "higher order" cuprates free from halide ions in the presence of boron trifluoride etherate as activating species. The most significant experimental results are reported in Table 1.

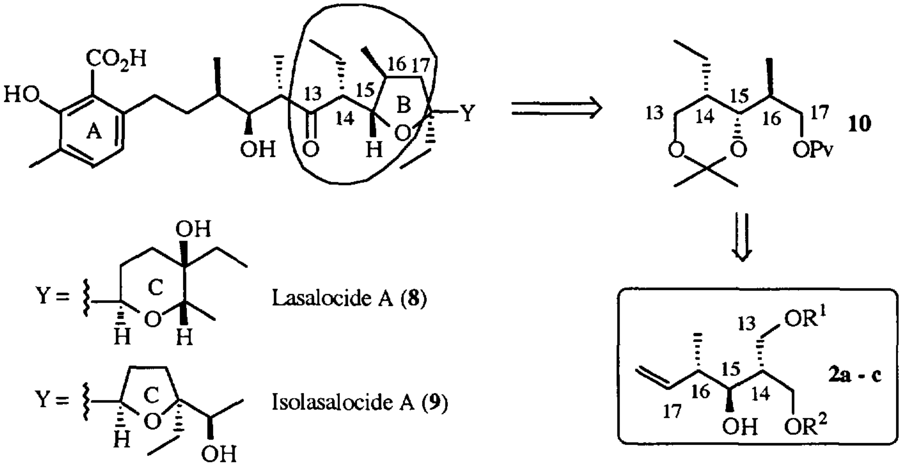
Alkene **4** was always formed as a by-product; a similar behaviour has already been observed by us,[4b] though mechanism of this reductive process has not been well understood.[6]

The "higher order" cuprate reagents[7] had always to be carefully preformed, in order to avoid *basic* instead of *nucleophilic* attack onto epoxide **1**. For example, if some amount of vinyllithium ("hard base") was still present when epoxide **1a** was added to the reaction mixture, alkene **7** was the only observed product, owed to basic attack on methyl protons ("hard acid") instead of nucleophilic attack on the oxiranic carbon atom ("soft acid").[8]

As already observed with simple alkyl cuprates,[4b] oxiranic ring opening generally occurred in acceptable to good chemical and regiochemical yields and both acetalic (benzyloxymethyl, BOM; 4-methoxybenzyloxymethyl, PMBOM) and ethereal (4-methoxyphenyl, PMP; triisopropylsilyl, TIPS; *t*-butyldimethylsilyl, TBDMS) protection were suitable for the two hydroxymethyl branches (entries 1 - 3). Only the TBDMS protecting group was cleaved to some extent under ring opening reaction conditions (entry 3). Monoprotected epoxide **1d** gave no positive result (entry 4). An attempt to test Grignard reagents in the presence of cuprous bromide[9] furnished, as the only detectable product, the corresponding bromohydrin, since, as already observed by us[4] and others,[10] epoxides are quite reactive with respect to halide ions under reaction conditions used for *C*-nucleophiles attack. Since, as already quoted in ref. 4b, some problem can arise using unprotected hydroxy epoxides, reactions of **1d** were not further explored.

Having in hand the strategy to obtain, in a diastereo- and enantioselective manner, the triols **2a - c**, we planned some utilisation in the filed of biologically active compounds.

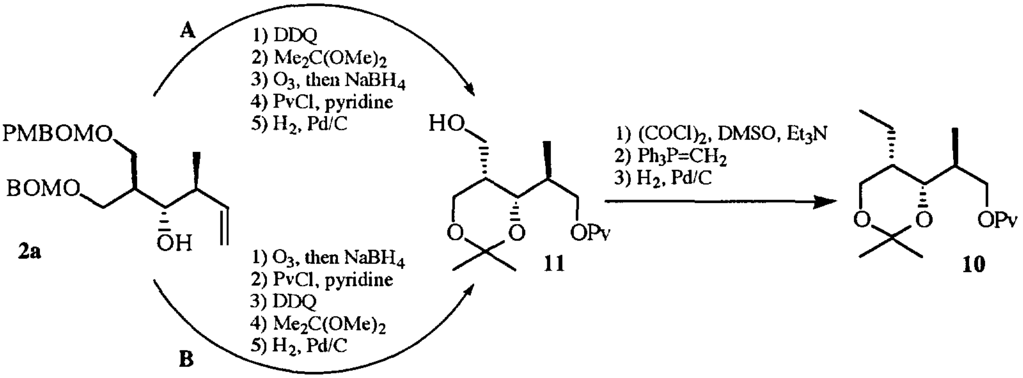
Polyether ionofore antibiotics are a class of very attracting targets.[11, 12a] The total synthesis of two polyether ionofore antibiotics, Lasalocide A (**8**) and isolasalocide A (**9**), has recently been reported.[13] The



Scheme 2

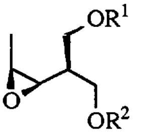
strategy followed involved the disconnection of the molecule into three fragments (C-1 - C-11, C-13 - C-17, and C-18 - C-24), which were independently synthesised from chiral precursors belonging to the natural "chiral pool" [(R)-(-)-citronellene,[11a] 1,2,5,6-diisopropylidene-D-glucose,[13a] and D-glucose or lactaldehyde,[13a] respectively] and finally assembled. Our building blocks **2a** - **c** seemed to be particularly suitable for the synthesis of the C-13 - C-17 fragment (**10**), that is involved in the formation of the tetrahydrofuran ring B (Scheme 2), and has been previously obtained from 1,2,5,6-diisopropylidene-D-glucose in about 11% yield (18 steps). The synthesis from **2** requires a few manipulations, not involving the already formed three chiral centres. Moreover, when this work was already completed, the same authors reported also the total convergent synthesis of another polyether ionofore antibiotic, lysocellin,[12] that employs an iodide derived from **10**[13b] to obtain the C-11 - C-15 subunit.

Several alternative routes can be though up to transform **2a** (the homoallylic alcohol which is obtained in better chemical and regiochemical yields starting from **1**) into **10**. Among them, route A was tried first to



Scheme 3

achieve (5-hydroxymethyl-2,2-dimethyl-1,3-dioxan-4-yl)-1-pivaloyloxypropane **11** (Scheme 3).



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Actually, removal of PMBOM under usual conditions^4 afforded a diol that, when reacted with acetone dimethyl ketal in the presence of traces of an acidic catalyst, furnished the corresponding 1,3-dioxane only in very poor yield (25%). The reason for this behaviour have not been completely understood, since a large number of very similar acetonides have been prepared in our laboratory.[14] Subsequent ozonolysis, followed by work up under reductive conditions, protection of the primary hydroxyl group as pivaloyl ester and removal of BOM protecting group through catalytic hydrogenolysis finally afforded **11**.

In an effort to improve the overall yield, arguing that the presence of the carbon - carbon double bond could be to a some extent responsible of poor results in the synthesis of dioxolane ring, steps 1 - 2 and 3 - 4 of the route A in Scheme 3 were reversed (route B). Ozonolysis of carbon - carbon double bond in **2a** afforded, after reductive work up, a diol, whose primary hydroxyl group could be selectively protected as pivaloyl ester.[15] After removal of PMBOM protecting group under usual conditions, the resulting diol could be transformed into a functionalised 1,3-dioxane in positively better yield (68%). Finally, catalytic hydrogenation afforded the unprotected primary alcohol **11**.

Elongation (one carbon atom) of the substituent in the position 5 of the dioxanic ring is the final task to accomplish to get **10**. Activation of hydroxyl to substitution as *p*-toluenesulfonyl ester and treatment with a cuprate reagent[14b] resulted in recovered tosylate ester (at low temperature) or its decomposition (at room temperature). On the contrary, oxidation of primary hydroxyl to aldehyde, Wittig condensation, and hydrogenation of the resulting alkene,[16] afforded the protected triol **10** (8 steps from **2a**, 35% overall yield).

An attempt to apply the same protocol to **2c** failed, since usual conditions applied to remove the PMBOM protecting group caused also, to a large extent, the removal of TBDMS protecting group.

It is noteworthy that, thanks to the high *enantio-* and *diastereodivergency* of THYM* and its derivatives, it is possible to obtain, following the same reaction pattern, both the enantiomer of **10** (starting from **1** or *ent*-**1**) and, in principle, both the enantiomers of its epimer at C-5 of the 1, 3-dioxane ring (C-14 of lasalocide A), starting from epoxide **12** or its enantiomer.[2]

Further applications of building blocks **2** in the field of antibiotics are being planned.

We wish to thank Mr. Alberto Moro for his helpful collaboration to this work and M.U.R.S.T. (40%) and C.N.R. for financial support.

EXPERIMENTAL

General. - NMR spectra (^{1}H and ^{13}C) were recorded as $CDCl_3$ solutions on a Varian Gemini 200 spectrometer at 200 MHz (^{1}H) and 50 MHz (^{13}C) using tetramethylsilane (TMS) as internal standards; chemical shifts (δ) are in ppm, coupling constants (*J*) are in Hertz (Hz); a * means that the value was obtained through double resonance experiments. Attribution of ^{13}C signals was made also with the aid of DEPT and HETCOR experiments. Optical rotatory powers ($[\alpha]_D$) were measured with a JASCO DIP 181 polarimeter as $CHCl_3$ solutions. IR spectra were recorded as $CHCl_3$ solutions on a Perkin Elmer 881 spectrometer. GC-MS were carried out on a HP-5971A instrument, using a HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 175°C. Analyses were performed with a constant He flow (0.9 ml/min), starting at 200°C for 2 min and then raising the temperature by 20°C/min up to 280°C (15 min).

'Usual workup' means that the given reaction mixture was extracted (Et_2O or AcOEt or CH_2Cl_2), the organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure.

Tetrahydrofuran (THF) was always freshly distilled from K / Ph_2CO; CH_2Cl_2, Et_2O, *N,N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were purchased as dry solvents from Aldrich and stored over 4 Å molecular sieves. Petroleum ether (PE) refers to the fraction boiling in the range 40 - 60°C.

PTSA stands for *p*-toluenesulfonic acid, DDQ for 2,3-dichloro-5,6-dicyanobenzoquinone.

All reactions requiring dry conditions were run under an inert atmosphere (N_2, unless otherwise stated).

TLC analyses were carried out on silica gel plates, which were observed under UV (254 nm) light and developed by dipping into a solution of 21 g of $(NH_4)_4MoO_4 \cdot 4H_2O$ and 1 g of $Ce(SO_4)_2 \cdot 4H_2O$ in 31 ml of H_2SO_4 and 469 ml of H_2O or a 2% aqueous solution of potassium permanganate and warming. R_f were measured after an elution of 7 - 9 cm. Column chromatographies were run following the method of 'flash chromatography',[17] using 230 - 400 mesh silica gel (Merck).

All compounds gave satisfactory spectroscopic and analytical data: an extensive selection of this data is reported.

Synthesis and spectroscopic and analytical data of optically active epoxides **1a, b, d** has been already reported,[2, 4a] as well as data of alkenes **4a, b**.[4a]

(2R, 3R, 4S)-1-(t-Butyldimethylsilyloxy)-2-[(4-methoxybenzyloxymethoxy)methyl]-3,4-epoxypentane 1c. - (2*S*, 3*R*, 4*S*)-2-[(4-Methoxybenzyloxymethoxy) methyl]-3,4-epoxypentan-1-ol[2] (1.0 mmol) was dissolved in anhydrous DMF (4 ml) at 0°C and added with imidazole (2.4 mmol) and *t*-butyldimethylsilylchloride (1.2 mmol). After stirring 1 h at room temperature, water (7 ml) was added. After usual workup (Et_2O) and chromatographic purification (PE / Et_2O 8 : 2 → 6 : 4, containing 0.5% of Et_3N), diprotected epoxide **1c** was obtained as a colourless oil (93%). $R_f = 0.32$ (PE / Et_2O 8 : 2). $[\alpha]_D = +9.5°$ (*c* 2). ^{1}H NMR: 0.06 & 0.07 (2 s, 3 H each, 2 x *Me*Si), 0.90 (s, 9 H, *Me*$_3$C), 1.31 (d, *J* 5.5, 3 H, *Me*CH), 1.61 - 1.76 [m, 1 H, C*H*(CH$_2$OR)$_2$], 2.93 (dd, *J* 4.3 & 9.5, 1 H, OC*H*CH), 3.12 (dq, *J* 4.4 & 5.5, 1 H, C*H*Me), 3.65 & 3.76 (AB part of an ABX system, *J* 5.5 & 6.8 & 9.7, 2 H, C*H*$_2$OR), 3.81 & 3.86 (AB part of an ABX system, *J* 0.8 & 4.2 & 10.0, 2 H, C*H*$_2$OR), 4.52 (s, 2 H, C*H*$_2$Ar), 4.72 (s, 2 H, OC*H*$_2$O), 6.86 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.29 (m, 2 H, Ar*H*).

General procedure for reaction of epoxides 1 with 'higher order' cuprates $(CH_2{=}CH)_2Cu(CN)Li_2$. - CuCN (5.0 mmol) was suspended in dry Et_2O (20 ml) under an inert atmosphere (He) and cooled to -78°C, then 17 ml of a 0.6 M solution of $CH_2{=}CHLi$ in Et_2O / hexane (10.0 mmol) were added and the reaction mixture was allowed to reach -10°C. The reaction mixture was cooled again to -78°C and a solution of the epoxide (0.5 mmol) in dry Et_2O (10 ml) was added, followed by the addition of 2.5 ml of a 0.4 M solution of $BF_3 \cdot Et_2O$ in dry Et_2O. After the appropriate reaction time at the temperature indicated in Table 1, 40 ml of 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v) were added, the reaction mixture was stirred at room temperature until two clear layers separated and worked up as usual (Et_2O). After column chromatography (PE / Et_2O), pure regioisomers **2** and **3** were isolated as colourless oils. Reaction yields and products ratios, as well as amount of by-products formed, can be found in Table 1.

For the experiment 4 of Table 1, reaction procedure was the same, but for the addition of $BF_3 \cdot Et_2O$ solution that was omitted.

2a: $R_f = 0.28$ (PE / Et_2O 6 : 4). $[\alpha]_D = -3.3°$ (*c* 2). Calculated for $C_{25}H_{34}O_6$: C% = 69.74, H% = 7.96. Found: C% = 71.01, H% = 7.92. ^{1}H NMR: 1.06 (d, *J* 6.9, 3 H, *Me*CH), 2.08 [app. sextuplet, *J* 5.3, 1 H, C*H*(CH$_2$OR)$_2$], 2.40 (app. sextuplet, *J* 7.2, 1 H, C*H*Me), 2.68 (d, *J* 4.6, 1 H, O*H;* disappeared after exchanging with D$_2$O), 3.56 - 3.64 (m, 1 H, C*H*OH; after exchanging with D$_2$O: 3.59, dd, *J* 4.9 & 6.7), 3.68 - 3.90 (m, 4 H, 2 x C*H*$_2$OR), 3.80 (s, 3 H, *Me*O), 4.53 (s, 2 H, C*H*$_2$Ar), 4.61 (s, 2 H, C*H*$_2$Ph), 4.73 & 4.76 (2 s, 2 H each, 2 x OC*H*$_2$O), 5.05 - 5.13 (m, 2 H, C*H*$_2$=CH), 5.79 - 5.97 (m, 1 H, C*H*=CH$_2$; *J** 9.6 & 18.0), 6.85 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.34 (m, 7 H, Ar*H*). ^{13}C NMR: 17.21 (*Me*CH), 41.33 & 41.71 [*C*HMe & *C*H(CH$_2$OR)$_2$], 55.24 (*Me*O), 66.21 & 67.52 & 69.16 & 69.61 (*C*H$_2$O & *C*H$_2$Ar), 75.18 (*C*HOH), 94.65 & 94.94 (O*C*H$_2$O), 113.87 & 127.76 & 127.84 & 128.45 & 129.49 (Ar*C*H), 115.53 (*C*H$_2$=), 129.86 & 137.72 & 159.31 (Ar*C*), 140.83 (*C*H=). IR (cm^{-1}): 3513, 2942, 1609, 1481, 1234, 1038. GC-MS: R$_t$ = 9.62 min; *m/z* (%): 309 (M$^+$ - 121, 0.4), 173 (4), 150 (12), 121 (100), 91 (37).

3a: R$_f$ = 0.14 (PE / Et$_2$O 6 : 4). ^{1}H NMR: 1.16 (d, *J* 6.3, 3 H, *Me*CH), 2.04 - 2.19 [m, 2 H, C*H*CH=CH$_2$ & C*H*(CH$_2$OR)$_2$], 3.14 (broad s, 1 H, O*H*; disappeared after exchanging with D$_2$O), 3.51 - 3.73 (m, 4 H, 2 x C*H*$_2$OR), 3.80 (s, 3 H, *Me*O), 3.94 - 4.08 (m, 1 H, C*H*OH; after exchanging with D$_2$O: 4.00, dq, *J* 2.6, & 6.3), 4.52 (s, 2 H, C*H*$_2$Ar), 4.61 (s, 2 H, C*H*$_2$Ph), 4.72 & 4.77 (2 s, 2 H each, 2 x OC*H*$_2$O), 5.08 (dd, *J* 2.2 & 17.2, 1 H, *H*CH=CH), 5.25 (dd, *J* 2.2 & 10.4, HC*H*=CH), 5.74 - 5.93 (m, 1 H, C*H*=CH$_2$; *J** 10.3 & 17.2), 6.85 - 6.90 (m, 2 H, Ar*H*), 7.24 - 7.34 (m, 7 H, Ar*H*). ^{13}C NMR: 21.25 (*Me*CH), 41.49 (*C*HCH$_2$), 51.55 (*C*HCH=), 55.30 (*Me*O), 67.08 & 68.26 & 69.25 & 69.72 (*C*H$_2$O & *C*H$_2$Ar), 67.58 (*C*HOH), 94.56 & 94.94 (O*C*H$_2$O), 113.88 & 127.76 & 127.83 & 128.45 & 129.52 (Ar*C*H), 119.33 (*C*H$_2$=), 135.27 (*C*H=), 137.72 & 141.26 & 159.31 (Ar*C*). IR (cm^{-1}): 3457, 2931, 1243, 1038.

2b: R$_f$ = 0.81 (PE / Et$_2$O 6 : 4). Calculated for $C_{24}H_{42}O_4Si$: C% = 68.20, H% = 10.02. Found: C% = 69.00, H% = 9.99. ^{1}H NMR: 1.03 - 1.08 (m, 24 H, 3 x C*HMe*$_2$ & *Me*CH), 2.08 - 2.20 [m, 1 H, C*H*(CH$_2$OR)$_2$], 2.37 - 2.55 (m, 1 H, C*H*Me), 3.16 (d, *J* 2.6, 1 H, O*H*), 3.70 - 3.77 (m, 1 H, C*H*OH), 3.77 (s, 3 H, *Me*O), 3.93 & 4.14 (AB part of an ABX system, *J* 4.1 & 4.2 & 9.8, 2 H, C*H*$_2$O), 4.18 (d, *J* 6.1, 2 H, C*H*$_2$O), 5.08 - 5.17 (m, 2 H, C*H*$_2$=), 5.90 (ddd, *J* 8.1 & 10.5, &16.9, 1 H, C*H*=), 6.84 (broad s, 4 H, Ar*H*). ^{13}C NMR: 11.84 (*C*HSi), 17.17 (*Me*CHCH), 17.94 (*Me*CHSi), 41.66 & 42.60 (*C*HMe & *C*HCH$_2$), 55.75 (*Me*O), 64.03 & 65.05 (*C*H$_2$O), 76.63 (*C*HOH), 114.61 & 115.35 (Ar*C*H), 115.52 (*C*H$_2$=), 141.30 (*C*H=), 153.04 & 153.81 (Ar*C*). IR (cm^{-1}): 3472, 2942, 1504, 1459, 1231, 1041.

3b: R$_f$ = 0.75 (PE / Et$_2$O 6 : 4). ^{1}H NMR: 1.06 - 1.10 (m, 21 H, 3 x C*HMe*$_2$), 1.16 (d, *J* 6.2, 3 H, *Me*CH), 2.16 - 2.29 [m, 2 H, C*H*(CH$_2$OR)$_2$ & C*H*CH=], 3.63 (broad s, 1 H, O*H*), 3.77 - 4.19 (m, 5 H, C*H*OH & 2 x C*H*$_2$O), 5.07 & 5.25 (AB part of an ABX system, *J* 2.3 & 10.3 & 17.2, 2 H, C*H*$_2$=), 5.93 (app. dt, *J* 9.9 & 17.1, 1 H, C*H*=), 6.83 (broad s, 4 H, Ar*H*). ^{13}C NMR: 11.93 (*C*HSi), 17.97 (*Me*CHSi), 21.34 (*Me*CH), 41.21 (*C*HCH$_2$), 51.84 (*C*HCH=), 55.81 (*Me*O), 62.01 & 68.77 (*C*H$_2$O), 68.29 (*C*HOH), 114.71 & 115.44 (Ar*C*H), 119.35 (*C*H$_2$=), 134.92 (*C*H=), 152.84 & 153.99 (Ar*C*).

2c: R$_f$ = 0.75 (PE / Et$_2$O 6 : 4). Calculated for $C_{23}H_{40}O_5Si$: C% = 65.05, H% = 9.49. Found: C% = 64.88, H% = 9.42. ^{1}H NMR: 0.08 (s, 6 H, 2 x *Me*Si), 0.90 (s, 9 H, *Me*$_3$C), 1.06 (d, *J* 6.9, 3 H, *Me*CH), 1.94 [app. sextuplet, *J* 5.2, 1 H, C*H*(CH$_2$OR)$_2$], 2.40 (app. sextuplet, *J* 6.9, 1 H, C*H*Me), 3.32 (d, *J* 4.9, 1 H, O*H*; disappeared after exchanging with D$_2$O), 3.55 - 3.63 (m, 1 H, C*H*OH; after exchanging with D$_2$O: 3.58, dd, *J* 5.1 & 6.3), 3.68 & 3.73 (AB part of an ABX system, *J* 5.1 & 6.5 & 9.7, 2 H, C*H*$_2$OR), 3.81 (s, 3 H, *Me*O), 3.89 & 3.93 (AB part of an ABX system, *J* 4.8 & 5.4 & 10.2, 2 H, CH$_2$OR), 4.53 (s, 2 H, CH$_2$Ar), 4.72 (s, 2 H, OCH$_2$O), 5.03 - 5.12 (m, 2 H, C*H*$_2$=), 5.93 (ddd, *J* 8.1 & 9.7 & 17.8, 1 H, C*H*=), 6.86 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.30 (m, 2 H, Ar*H*). IR (cm^{-1}): 3479, 2957, 2930, 1611, 1463, 1226, 1034.

3c: R$_f$ = 0.75 (PE / Et$_2$O 6 : 4). ^{1}H NMR: 0.08 (s, 6 H, 2 x *Me*Si), 0.90 (s, 9 H, *Me*$_3$C), 1.14 (d, *J* 6.6, 3 H, *Me*CH), 3.41 (d, *J* 6.9, 1 H, O*H*; disappeared after exchanging with D$_2$O), 3.45 - 4.04 (m, 5 H, C*H*OH & 2 x C*H*$_2$OR), 3.82 (s, 3 H, *Me*O), 4.53 (s, 2 H, C*H*$_2$Ar), 4.74 (s, 2 H, OC*H*$_2$O), 4.97 - 5.05 (m, 2 H, C*H*$_2$=), 5.71 (ddd, *J* 8.5 & 10.1 & 17.3, 1 H, C*H*=), 6.86 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.30 (m, 2 H, Ar*H*); signals due to C*H*Me and C*H*(CH$_2$OR)$_2$ are obscured by signals from **2c**.

Spectral data of by-products are reported below.

4c: R_f = 0.86 (PE / Et_2O 6 : 4). ^{1}H NMR: 0.04 (s, 6 H, 2 x *Me*Si), 0.89 (s, 9 H, *Me*$_3$C), 1.67 (dd, *J* 1.7 & 6.8, 3 H, *Me*CH), 2.75 - 2.92 [m, 1 H, C*H*(CH$_2$OR)$_2$], 3.55 & 3.67 (AB part of an ABX system, *J* 6.0 & 6.1 & 9.4, 2 H, C*H*$_2$O), 3.59 (d, *J* 5.9, 2 H, C*H*$_2$O), 3.81 (s, 3 H, *Me*O), 4.52 (s, 2 H, C*H*$_2$Ar), 4.73 (s, 2 H, OC*H*$_2$O), 5.33 (app. tq, *J* 1.7 & 11.0, 2 H, C*H*$_2$=), 5.53 - 5.72 (m, 1 H, C*H*=), 6.86 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.30 (m, 2 H, Ar*H*). ^{13}C NMR: 13.33 (*Me*Si), 18.33 (*Me*CH=), 25.93 (*Me*CSi), 40.29 [*C*H(CH$_2$OR)$_2$], 55.28 (*Me*O), 63.37 & 68.82 & 68.88 (*C*H$_2$Ar & *C*H$_2$O), 94.54 (O*C*H$_2$O), 113.85 (ArC*H*), 126.41 & 129.04 (*C*H=*C*H), 129.56 (Ar*C*H), 130.13 & 159.25 (Ar*C*). IR (cm^{-1}): 2928, 1604, 1251, 1034.

6: R_f = 0.50 (PE / Et_2O 6 : 4). ^{1}H NMR: 0.08 (s, 6 H, 2 x *Me*Si), 0.90 (s, 9 H, *Me*$_3$C), 1.14 (d, *J* 6.4, 3 H, *Me*CH), 1.92 - 2.18 [m, 2 H, C*H*Me & C*H*(CH$_2$OR)$_2$], 3.47 - 4.05 (m, 5 H, 2 x C*H*$_2$OR & C*H*OH), 3.81 (s, 3 H, *Me*O), 4.52 (s, 2 H, C*H*$_2$Ar), 4.70 & 4.72 (AB system, *J* 6.8, 2 H, OC*H*$_2$O), 5.05 (dd, *J* 2.3 & 17.4, 1 H, CH*H*=), 5.21 (dd, *J* 2.3 & 10.4, 1 H, C*H*H=), 5.86 (dt, *J* 7.1 & 10.1, 1 H, C*H*=), 6.86 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.30 (m, 2 H, Ar*H*). IR (cm^{-1}): 3429, 2952, 2928, 1609, 1461, 1036.

7: R_f = 0.29 (PE / Et_2O 6 : 4). ^{1}H NMR: 2.02 - 2.25 [m, 1 H, C*H*(CH$_2$OR)$_2$], 2.64 (d, *J* 4.2, 1 H, O*H*; disappeared after D_2O exchange), 3.63 - 3.73 (m, 1 H, C*H*OH), 3.67 & 3.72 (AB part of an ABX system, *J* 1.8 & 3.0 & 7.2, 2 H, C*H*$_2$OR), 3.82 & 3.87 (AB part of an ABX system, *J* 3.5 & 3.9 & 8.6, 2 H, C*H*$_2$OR), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, C*H*$_2$Ar), 4.61 (s, 2 H, C*H*$_2$Ph), 4.72 & 4.76 (2 s, 2 H each, 2 x OC*H*$_2$O), 5.06 & 5.16 (AB part of an ABX system, *J* 2.1 & 10.3 & 17.2, 2 H, C*H*$_2$=CH), 5.74 (ddd, *J* 9.3 & 10.3 & 17.2, 1 H, C*H*=CH$_2$), 6.84 - 6.91 (m, 2 H, Ar*H*), 7.24 - 7.36 (m, 7 H, Ar*H*). ^{13}C NMR: 47.66 (*C*HCH$_2$), 55.03 (*Me*O), 66.72 & 66.84 & 68.90 & 69.36 (*C*H$_2$O & *C*H$_2$Ar), 73.40 (*C*HOH), 94.43 & 94.73 (O*C*H$_2$O), 116.94 (*C*H$_2$=), 113.69 & 127.55 & 127.66 & 128.25 & 129.29 (Ar*C*H), 129.72 & 137.59 & 159.13 (Ar*C*), 138.95 (*C*H=). IR (cm^{-1}): 3514, 2898, 1611.

Reaction of monoprotected epoxide 1d with Grignard reagent in the presence of copper(I) bromide. - A mixture of CuBr·Me_2S (1.0 mmol) and Me_2S (1.2 ml) in dry Et_2O (4 ml) under an inert atmosphere (He) was cooled to -20°C and added with 2.5 ml of a 1 M solution of vinylmagnesium bromide in THF (2.5 mmol). After 10 min, a solution of epoxide **1d** (0.3 mmol) in dry E_2O (5 ml) was added. After stirring 24 h at -20°C and 5 h at room temperature, 20 ml of 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v) were added, the reaction mixture was stirred at room temperature until two clear layers separated and worked up as usual (Et_2O). Only traces of bromohydrin **5** (4%) were observed, along with unidentified by-products. R_f = 0.32 (PE / Et_2O 1 : 1). ^{1}H NMR: 1.03 - 1.07 (m, 21 H, 3 x C*HMe*$_2$), 1.78 (d, *J* 6.2, 3 H, *Me*CH), 1.88 - 2.01 [m, 1 H, C*H*(CH$_2$OR)$_2$], 3.69 - 3.74 (m, 1 H, C*H*OH; *J** 4.4 & 6.3), 3.84 - 4.00 (m, 4 H, 2 x C*H*$_2$OR), 4.43 (dq, *J* 4.4 & 6.2, 1 H, C*H*Me). ^{13}C NMR: 12.16 (*C*Si), 17.82 (SiCH*Me*$_2$), 22.89 (*Me*CHBr), 46.19 [*C*H(CH$_2$OR)$_2$], 56.01 (*C*HBr), 62.54 & 63.45 (*C*H$_2$O), 74.85 (*C*HOH).

(2R, 3S, 4S)-2-[(Benzyloxymethoxy)methyl]-4-methylhex-5-en-1,3-diol. - A solution of **2a** (1.0 mmol) in CH_2Cl_2 (14 ml) was added with 1.4 ml of a 0.1 M pH 7 phosphate buffer and 1.4 ml of *t*-BuOH and treated with 2.4 mmol of DDQ at room temperature. After 4 h, a saturated aqueous solution of $NaHCO_3$ was added, the organic phase was separated and the aqueous phase extracted (CH_2Cl_2). The recombined organic layers were washed with 5% $NaHSO_3$ aqueous solution, then with a saturated $NaHCO_3$ aqueous solution and finally dried, filtered and evaporated to dryness. Column chromatography (PE / Et_2O 4 : 6 → 2 : 8, containing 0.5% of Et_3N) afforded pure diol (80%). R_f = 0.40 (PE / Et_2O 2 : 8). ^{1}H NMR: 1.05 (d, *J* 6.7, 3 H, *Me*CH), 1.91 - 2.03 [m, 1 H, C*H*(CH$_2$OR)$_2$], 2.29 - 2.47 (m, 3 H, 2 x CHO*H* & C*H*Me; after exchanging with D_2O: 2.38, app. sextuplet, *J* 7.0, 1 H), 3.54 - 3.67 (m, 1 H, C*H*OH; after exchanging with D_2O: 3.60, dd, *J* 4.5 & 7.5), 3.81 - 3.97 [m, 4 H, 2 x C*H*$_2$O; after exchanging with D_2O: 3.83 & 3.92 (AB part of an ABX system, *J* 2.0 & 6.8 & 11.9, 2 H, C*H*$_2$OH) & 3.87 (app. d, *J* 4.5, 2 H, C*H*$_2$OR)], 4.63 (s, 2 H, C*H*$_2$Ph), 4.79 (s, 2 H, OCH_2O), 5.08 - 5.17 (m, 2 H, CH_2=), 5.69 - 5.86 (m, 1 H, CH=), 7.32 - 7.37 (m, 5 H, *Ph*). IR (cm^{-1}): 3522, 2936, 1454, 1379, 1038.

(4S, 5S, 1'S)-5-[(Benzyloxymethoxy)methyl]-2,2-dimethyl-4-(1'-methylprop-2'-enyl)-1,3-dioxane. - A solution of 1.0 mmol of (2*R*, 3*S*, 4*S*)-2-[(benzyloxymethoxy)methyl]-4-methylhex-5-en-1,3-diol in dry CH_2Cl_2 (18 ml) was cooled to 0°C and treated with 3.0 mmol of 2-methoxypropene and 71 μl of a 0.2 M solution of PTSA in THF (0.01 mmol). After stirring 10 min at the same temperature, Et_3N (0.2 ml) was added and solvent was evaporated under reduced pressure. Chromatographic purification (PE / Et_2O 95 : 5 → 9 : 1) afforded pure 1,3-dioxane (25%). ^{1}H NMR: 1.05 (d, *J* 6.8, 3 H, *Me*CH), 1.32 & 1.32 (2 s, 3 H each, Me_2C), 2.04 - 2.19 (m, 1 H, C*H*CH_2OBOM), 2.47 - 2.64 (m, 1 H, C*H*Me), 3.45 (d, *J* 5.9, 2 H, CH_2O), 3.57 & 3.78 (AB part of an ABX system, *J* 4.2 & 6.9 & 9.7, 2 H, CH_2O), 4.20 (dd, *J* 4.6 & 7.1, 1 H, C*H*O), 4.59 (s, 2 H, CH_2Ph), 4.71 & 4.74 (AB system, *J* 6.6, 2 H, OCH_2O), 4.98 - 5.10 (m, 2 H, CH_2=), 5.88 (ddd, *J* 8.2 & 10.4 & 17.1, 1 H, C*H*=), 7.31 - 7.37 (m, 5 H, Ar*H*). IR (cm^{-1}): 3488, 2996, 1387, 1205, 1047.

(4S, 5S, 1'S)-5-[(Benzyloxymethoxy)methyl]-2,2-dimethyl-4-(1'-methyl-2'-hydroxyethyl)-1,3-dioxane. - A solution of (4*S*, 5*S*, 1'*S*)-5-[(benzyloxymethoxy)methyl]-2,2-dimethyl-4-(1'-methylprop-2'-enyl)-1,3-dioxane (1.0 mmol) in dry MeOH (6.5 ml) and dry CH_2Cl_2 (4 ml) was cooled to -78°C and ozone was bubbled into the solution until persistence of a grey - blue colour. After further bubbling of oxygen for 5 min, the flask was put under an inert atmosphere (N_2) and Me_2S (0.5 ml) was added. After 5 min, $NaBH_4$ (7.3 mmol) was rapidly added as a solid and reaction temperature was allowed to reach -15°C. After stirring 30 min at the same temperature, a saturated aqueous solution of NH_4Cl (6 ml) was added and most of organic solvent was evaporated under reduced pressure. Usual workup of aqueous phase (Et_2O) and chromatography (PE / Et_2O 8 : 2 → 2 : 8, containing 0.5% of Et_3N) afforded the desired product (95%). ^{1}H NMR: 1.04 (d, *J* 7.0, 3 H, *Me*CH), 1.31 & 1.33 (2 s, 3 H each, Me_2C), 1.89 - 2.07 (m, 1 H, C*H*Me), 2.19 - 2.34 (m, 1 H, C*H*CH_2OBOM), 2.50 (t, *J* 6.9, 1 H, O*H*; disappeared after exchanging with D_2O), 3.27 - 3.80 (m, 6 H, 3 x CH_2O), 4.60 (s, 2 H, CH_2Ph), 4.73 & 4.76 (AB system, *J* 6.8, 2 H, OCH_2O), 5.12 (dd, *J* 3.6 & 8.7, 1 H, C*H*O), 7.33 - 7.37 (m, 5 H, Ar*H*). IR (cm^{-1}): 3499, 2933, 1730, 1187, 1040.

(4*S*, 5*S*, 1'*S*)-5-[*(Benzyloxymethoxy)methyl]-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-1,3-dioxane.*

From (4S, 5S, 1'S)-5-[(benzyloxymethoxy)methyl]-2,2-dimethyl-4-(1'-methyl-2'-hydroxyethyl)-1,3-dioxane. - A solution of substrate (0.1 mmol) in dry pyridine (0.5 ml) was cooled to 0°C and added with 0.3 mmol of Me_3CCOCl. After stirring 24 h at room temperature, reaction mixture was diluted with water and Et_2O and subjected to usual workup (Et_2O). After chromatographic purification (PE / Et_2O 8 : 2 → 7 : 3, containing 0.5 % of Et_3N), pure product was obtained (95%). R_f = 0.57 (PE / Et_2O 6 : 4). $[\alpha]_D$ = -9.3 (*c* 0.5). ^{1}H NMR: 0.94 (d, *J* 6.8, 3 H, *Me*CH), 1.21 (s, 9 H, Me_3C), 1.36 & 1.41 (2 s, 3 H each, Me_2C), 1.68 - 1.75 (m, 1 H, C*H*CH_2OBOM), 1.84 - 1.96 (m, 1 H, C*H*Me), 3.68 - 4.14 (m, 7 H, 3 x CH_2O & C*H*O), 4.60 & 4.63 (AB system, *J* 11.8, 2 H, CH_2Ph), 4.79 (s, 2 H, OCH_2O), 7.31 - 7.37 (m, 5 H, Ar*H*). ^{13}C NMR: 12.38 (*Me*CH), 18.83 & 29.65 (*Me*C), 27.29 (*Me*CC=O), 34.41 & 35.29 (*C*HMe & *C*HCH_2OBOM), 38.97 (*C*C=O), 62.08 & 63.15 & 66.75 & 69.47 (CH_2O & CH_2Ph), 71.42 (*C*HO), 94.94 (OCH_2O), 98.91 (O*C*O), 127.71 & 127.98 & 128.42 (ArCH), 137.92 (Ar*C*), 178.51 (*C*=O). GC-MS: R_t = 5.41 min; *m/z* (%): 393 (M^+ - 15, 5), 171 (7), 149 (14), 91 (100). IR (cm^{-1}): 3487, 2931, 1721, 1610, 1454, 1380, 1246, 1029.

From (2SR 3S, 4S)-2-[(benzyloxymethoxy)methyl]-4-methyl-5-(trimethylacetoxy)pentane-1,3-diol. - To a solution of substrate (1.0 mmol) in dry CH_2Cl_2 (13 ml), cooled to 0°C, 2-methoxypropene (1.9 mmol) and 71 μl of a 0.2 M solution of PTSA in THF were added. After stirring 10 min at the same temperature, Et_3N

(0.2 ml) was added and solvent was evaporated under reduced pressure. Chromatographic purification (PE / AcOEt 95 : 5, containing 0.5% of Et$_3$N) afforded pure product (68%).

(2S, 3S, 4S)-4-[(Benzyloxymethoxy)methyl]-2-methyl-5-[(4-methoxybenzyloxy)methoxy]pentane-1,3-diol. - Homoallylic alcohol **2a** was ozonized as above described for (4*S*, 5*S*, 1'*S*)-5-[(benzyloxymethoxy)-methyl]-2,2-dimethyl-4-(1'-methylprop-2'-enyl)-1,3-dioxane. Chromatographic purification (Et$_2$O, containing 0.5 % of Et$_3$N) afforded pure diol (66%). R$_f$ = 0.49 (Et$_2$O). $[\alpha]_D$ = +4.9° (*c* 1.2). ^{1}H NMR: 0.83 (d, *J* 6.9 3 H, *Me*CH), 1.90 - 2.09 [m, 2 H, C*H*Me & C*H*(CH$_2$OR)$_2$], 3.58 - 3.96 (m, 7 H, 2 x C*H*$_2$OR & C*H*$_2$OH & C*H*OH), 3.80 (s, 3 H, *Me*O), 4.54 (s, 2 H, C*H*$_2$Ar), 4.60 (s, 2 H, C*H*$_2$Ph), 4.75 & 4.76 (2 s, 2 H each, 2 x OC*H*$_2$O), 6.86 - 6.90 (m, 2 H, Ar*H*), 7.25 - 7.36 (m, 7 H, Ar*H*). GC-MS: R$_t$ = 12.24 min: *m*/*z* (%): 298 (M$^+$ - 136, 0.3), 177 (24), 150 (21), 137 (42), 121 (100), 91 (42).

(2S, 3S, 4S)-1-(Benzyloxymethoxy)-2-[(4-methoxybenzyloxymethoxy)methyl]-4-methyl-5-(trimethylacetoxy)pentan-3-ol. - To a solution of diol (1.0 mmol) in dry pyridine (3 ml), cooled to 0°C, 2.3 mmol of Me$_3$CCOCl were added. After stirring 5 h, *n*-heptane was added and the reaction mixture was evaporated to dryness. Chromatographic purification (PE / AcOEt 1 : 1, containing 0.5% of Et$_3$N) afforded pure monoester (85%). R$_f$ = 0.86 (PE / AcOEt 1 : 1). $[\alpha]_D$ = -4.5° (*c* 1.3). ^{1}H NMR: 0.95 (d, *J* 6.9, 3 H, *Me*CH), 1.21 (s, 9 H, *Me*$_3$C), 1.92 - 2.14 [m, 2 H, C*H*Me & C*H*(CH$_2$OR)$_2$], 3.03 (d, *J* 5.9, 1 H, O*H*; disappeared after exchanging with D$_2$O), 3.59 - 4.00 (m, 5 H, 2 x C*H*$_2$OR & C*H*OH), 3.80 (s, 3 H, *Me*O), 4.16 & 4.27 (AB part of an ABX system, *J* 3.8 & 6.2 & 10.9, 2 H, C*H*$_2$OPv), 4.53 (s, 2 H, C*H*$_2$Ar), 4.60 (s, 2 H, C*H*$_2$Ph), 4.74 & 4.75 (2 s, 2 H each, 2 x OC*H*$_2$O), 6.85 - 6.89 (m, 2 H, Ar*H*), 7.24 - 7.35 (m, 7 H, Ar*H*). IR (cm^{-1}): 3515, 2950, 1717, 1479, 1173, 1041. GC-MS: R$_t$ = 16.83 min; *m*/*z* (%): 275 (M$^+$ - 243, 0.3), 261 (10), 150 (23), 137 (24), 121 (100), 91 (43).

(2R, 3S, 4S)-2-[(Benzyloxymethoxy)metil]-4-methyl-5-(trimethylacetoxy)pentane-1,3-diol. - The PMBOM protecting group was removed as above described for **2a**. After chromatographic purification (PE / AcOEt, containing 0.5% of Et$_3$N), the pure diol was obtained (79%). R$_f$ = 0.65 (PE / AcOEt 3 : 7). $[\alpha]_D$ = +0.5° (*c* 1.3). ^{1}H NMR: 0.96 (d, *J* 6.9, 3 H, *Me*CH), 1.20 (s, 9 H, *Me*$_3$C), 1.86 - 2.10 [m, 2 H, C*H*Me & C*H*(CH$_2$OR)$_2$], 3.57 - 3.66 (m, 1 H, C*H*OH; after exchanging with D$_2$O: 3.61, dd, *J* 3.4 & 9.1), 3.72 - 4.04 (m, 4 H, C*H*$_2$OR & C*H*$_2$OH), 4.16 & 4.27 (AB part of an ABX system, *J* 4.0 & 5.4 & 11.1, 2 H, C*H*$_2$OPv), 4.62 (s, 2 H, C*H*$_2$Ph), 4.77 (s, 2 H, OC*H*$_2$O), 7.30 - 7.36 (m, 5 H, Ar*H*). ^{13}C NMR: 14.12 (*Me*CH), 27.22 (*Me*CC=O), 36.68 & 41.67 (*C*HCH$_2$OH & *C*HMe), 38.93 (*C*C=O), 63.95 & 65.57 & 66.58 & 69.87 (*C*H$_2$O & *C*H$_2$Ph), 95.11 (O*C*H$_2$O), 127.83 & 128.47 (Ar*C*H), 137.63 (Ar*C*), 179.07 (*C*=O). IR (cm^{-1}): 3509, 2956, 1715, 1467, 1154, 1043. GC-MS: R$_t$ = 5.66 min; *m*/*z* (%): 261 (M$^+$ - 107, 2), 195 (4), 173 (6), 91 (100).

(4S, 5S, 1'S)-5-Hydroxymethyl-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-1,3-dioxane 11. - A solution of 0.1 mmol of (4*S*, 5*S*, 1'*S*)-5-[(benzyloxymethoxy)methyl]-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-1,3-dioxane in MeOH (7 ml), containing 30 mg of CaCO$_3$, was hydrogenated for 8 h at room temperature and normal pressure in the presence of a catalytic amount of 10% palladium on activated charcoal. Filtration (washing the residue with AcOEt) and evaporation of the solvent afforded pure **11** (quantitative yield). R$_f$ = 0.10 (PE / Et$_2$O 6 : 4). ^{1}H NMR: 0.96 (d, *J* 6.8, 3 H, *Me*CH), 1.21 (s, 9 H, *Me*$_3$C), 1.37 & 1.42 (2 s, 3 H each, 2 x *Me*CO), 1.60 -1.68 (m, 1 H, C*H*CH$_2$OH), 1.87 - 2.05 (m, 1 H, C*H*Me), 3.77 - 4.15 (m, 7 H, 3 x C*H*$_2$O & C*H*O). GC-MS: R$_t$ = 5.41 min; *m*/*z* (%): 167 (M$^+$ - 121, 39), 149 (100), 91 (46).

(4S, 5S, 1'S)-2,2-Dimethyl-5-formyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-1,3-dioxane. - To 1.7 ml of a 0.15 M solution of $(COCl)_2$ in CH_2Cl_2 (0.26 mmol), cooled to -78°C, 0.20 ml of a 2 M solution of DMSO in CH_2Cl_2 (0.40 mmol) were added. After stirring 15 min at the same temperature, 0.1 mmol of **11** were added as a CH_2Cl_2 (1 ml) solution and, after additional 15 min, 0.60 mmol of Et_3N were added. After stirring 3 h at -78°C, 3 ml of a 5% aqueous solution of $NH_4H_2PO_4$ were added. Usual workup (Et_2O) afforded the aldehyde (quantitative yield) sufficiently pure to be used crude in the following step. R_f = 0.45 (PE / Et_2O 6 : 4). ^1H NMR: 0.96 (d, *J* 6.9, 3 H, *Me*CH), 1.21 (s, 9 H, *Me*$_3$C), 1.43 & 1.48 (2 s, 3 H each, 2 x *Me*CO), 1.90 - 2.22 (m, 2 H, MeC*H* & C*H*CHO), 3.93 - 4.18 (m, 5 H, 2 x C*H*$_2$O & C*H*O), 10.11 (d, *J* 3.7, 1 H, C*H*O).

(4S, 5S, 1'S)-2,2-Dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-5-vinyl-1,3-dioxane. - To a solution of (4*S*, 5*S*, 1'*S*)-2,2-dimethyl-5-formyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-1,3-dioxane (0.1 mmol) in dry THF (3 ml) cooled to -78°C, an excess (about 3 eq) of a freshly prepared solution of (methylidene)triphenylphosphorane in dry THF was added until yellow colour persisted. Reaction mixture was allowed to reach room temperature and filtered washing with PE, in order to remove most of Ph_3PO. Crude product was chromatographated (PE / Et_2O 9 : 1) to give pure alkene. R_f: 0.70 (PE / Et_2O 3 : 1). ^1H NMR: 0.87 (d, *J* 6.8, 3 H, *Me*CH), 1.21 (s, 9 H, *Me*$_3$C), 1.39 (s, 3 H, *Me*C), 1.42 (s, 3 H, *Me*C), 1.50 -2.15 (m, 2 H, MeC*H* & C*H*CH=), 3.72 & 3.78 (AB part of an ABX system, *J* 2.3 & 2.3 & 5.1, 2 H, C*H*$_2$O), 4.05 & 4.15 (AB part of an ABX system, *J* 2.8 & 4.5 & 15.4, 2 H, PvOC*H*$_2$), 4.53 - 4.79 (m, 1 H, C*H*O), 5.11 - 5.22 (m, 2 H, C*H*$_2$=CH), 6.26 (ddd, *J* 9.8 & 10.7 & 17.0, 1 H, CH$_2$=C*H*).

(4S, 5S, 1'S)-2,2-Dimethyl-5-ethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-1,3-dioxane 10. - A solution of (4*S*, 5*S*, 1'*S*)-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-5-vinyl-1,3-dioxane (0.1 mmol) in absolute EtOH (5 ml) was hydrogenated for 4 h at room temperature and normal pressure in the presence of a catalytic amount of 10% palladium on activated charcoal. Filtration and evaporation of the solvent afforded pure **10** (46% overall yield from **11**, three steps), whose spectral and analytical data were consistent with reported data.[13b] $[\alpha]_D$ = -8.0° (*c* 0.4).

(4S, 5R, 1'S)-2,2-Dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]--5-[(p-toluenesulfonyloxy)methyl]-1,3-dioxane. - To a solution of **11** (0.05 mmol) in dry CH_2Cl_2 (4 ml) cooled to 0°C were sequentially added 0.5 mmol of Et_3N and 0.25 mmol of *p*-toluenesulfonyl chloride. After stirring 24 h at room temperature, a second aliquot of reagents (0.5 ml of Et_3N and 0.25 mmol of *p*-toluenesulfonyl chloride) was added at 0°C and reaction mixture stirred at room temperature for additional 24 h. Saturated aqueous NH_4Cl (1 ml) was added and the usual workup was applied (CH_2Cl_2). After chromatographic purification, the tosylate was obtained as a white solid (49%). R_f = 0.49 (PE / Et_2O 6 : 4). $[\alpha]_D$ = +14.2° (*c* 0.7); ^1H NMR: 0.91 (d, *J* 6.8, 3 H, *Me*CH), 1.20 (s, 9 H, *Me*$_3$C), 1.22 & 1.35 (2 s, 3 H each, 2 x *Me*CO), 1.66 - 1.90 (m, 2 H, MeC*H* & C*H*CHO), 2.45 (s, 3 H, *Me*Ar), 3.78 (dd, *J* 2.3 & 10.5, 1 H, C*H*O), 3.92 - 4.09 (m, 4 H, 2 x C*H*$_2$O), 7.34 - 7.38 (m, 2 H, Ar*H*), 7.79 - 7.83 (m, 2 H, Ar*H*).

Attempted reaction of (4S, 5R, 1'S)-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-5-[(p-toluenesulfonyloxy)methyl]-1,3-dioxane with a cuprate reagent.

Using lithium dimethylcuprate. - A suspension of CuI (2.0 mmol) in dry Et_2O (2 ml) cooled to -10°C under an inert atmosphere (He) was added with 2.5 ml of a 1.6 M solution of MeLi in Et_2O (4.0 mmol) and stirred for 10 min at the same temperature. An aliquot of this solution (2.3 ml, about 1 mmol of Me_2CuLi) was added to a solution of (4*S*, 5*R*, 1'*S*)-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-5-[(*p*-toluenesulfonyloxy)methyl]-1,3-dioxane (0.1 mmol) in dry Et_2O (5 ml) cooled to -50°C. After stirring for 24 h at room temperature, only substrate was detectable in the reaction mixture. When cuprate / tosylate ratio was raised, decomposition of substrate took place, but desired product was never observed.

Using lithium dimethylcyanocuprate. - A suspension of CuCN (2.0 mmol) in dry Et_2O (2 ml) cooled to -65°C under an inert atmosphere (Ar) was added with 2.5 ml of a 1.6 M solution of MeLi in Et_2O (4.0 mmol) and the reaction mixture was allowed to reach 0°C. An aliquot of this solution (2.3 ml, about 1 mmol of $Me_2CuCNLi_2$) was added to a solution of (4*S*, 5*R*, 1'*S*)-2,2-dimethyl-4-[1'-methyl-2'-(trimethylacetoxy)ethyl]-5-[(*p*-toluenesulfonyloxy)methyl]-1,3-dioxane (0.1 mmol) in dry Et_2O (2 ml) cooled to -65°C. After stirring for about 20 h at room temperature, only by-products were detectable in the reaction mixture.

(2R, 3S, 4S)-2-[(t-Butyldimethylsilyloxy)methyl]-4-methylhex-5-ene-1,3-diol. - A solution of **2b** (1.0 mmol) in CH_2Cl_2 (20 ml) was added with 3.3 ml of a 0.1 M pH 7 phosphate buffer and 2.7 ml of *t*-BuOH and treated with 1.7 mmol of DDQ at room temperature. After 24 h, 2.9 mmol of DDQ were added, and reaction mixture stirred for additional 2 h. A saturated aqueous solution of $NaHCO_3$ was added, the organic phase was separated and the aqueous phase extracted (CH_2Cl_2). The recombined organic layers were washed with a freshly prepared 5% $NaHSO_3$ aqueous solution, then with a saturated $NaHCO_3$ aqueous solution and finally dried, filtered and evaporated to dryness. Column chromatography (PE / Et_2O 8 : 2 → 6 : 4, containing 0.5% of Et_3N) afforded pure diol (14%). R_f = 0.43 (PE / Et_2O 6 : 4). ^1H NMR: 0.10 (s, 6 H, 2 x *Me*Si), 0.91 (s, 9 H, Me_3C), 1.07 (d, *J* 6.8, 3 H, *Me*CH), 1.78 - 1.91 [m, 1 H, $CH(CH_2OR)_2$], 2.36 - 2.48 (m, 1 H, C*H*Me), 2.56 (d, *J* 4.8, 1 H, O*H*; disappeared after exchanging with D_2O), 3.56 - 3.65 (m, 1 H, C*H*OH; after exchanging with D_2O: 3.59, dd, *J* 5.3 & 6.9), 3.76 - 4.09 (m, 4 H, 2 x CH_2O), 5.01 - 5.16 (m, 2 H, CH_2=), 5.64 - 5.92 (m, 1 H, C*H*=). IR (cm^{-1}): 3483, 2940, 1251, 1071.

Spectroscopic data for (3*S*, 4*S*)-2-(hydroxymethyl)-4-methylhex-5-ene-1,3-diol (white solid): ^1H NMR: 1.04 (d, *J* 6.8, 3 H, *Me*CH), 1.77 - 1.90 [m, 1 H, $CH(CH_2OH)_2$], 2.33 - 2.52 (m, 1 H, C*H*Me), 3.61 - 4.09 (m, 5 H, C*H*OH & 2 x CH_2OH), 5.00 - 5.20 (m, 2 H, CH_2=), 5.61 - 5.88 (m, 1 H, C*H*=). IR (cm^{-1}): 3457, 2976, 1395, 1192, 1045.

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5. Actually, thank to enantiodivergency of THYM* derivatives, either enantiomeric form of epoxides **1** were used at times in this work, but, for sake of simplicity, the same enantiomer is generally used in Schemes and discussion.
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