Chemoenzymatic Preparation of Asymmetrized Tris(hydroxymethyl)methane (THYM*) and of Asymmetrized Bis(hydroxymethyl)acetaldehyde (BHYMA*) as New Highly Versatile Chiral Building Blocks[1]

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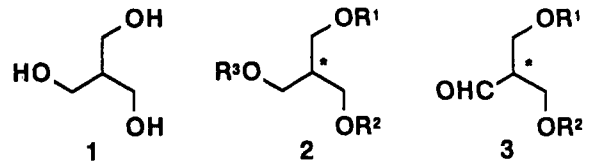
A series of asymmetrized tris(hydroxymethyl)methanes **2** and bis(hydroxymethyl)acetaldehydes **3** have been prepared in both enantiomeric forms through a chemoenzymatic methodology. The key step is the highly enantioselective PPL-catalyzed monohydrolysis of 2(*E*)-alkenyl-1,3-diacetoxypropanes **25–27**. A careful study on the effect of unsaturations adjacent to the prochiral center in a series of 2-substituted 1,3-diacetoxypropanes has confirmed the suggested beneficial effect of a π system in that position but has also unveiled an unprecedented dramatic effect of double-bond configuration on enantioselectivity. A new empirical model for the interpretation of these and other results, based both on polarity and steric arguments, is proposed. This study provides a general protocol for the efficient synthesis of asymmetrized 1,3-propanediols bearing in position 2 saturated or unsaturated carbon chains.

Introduction

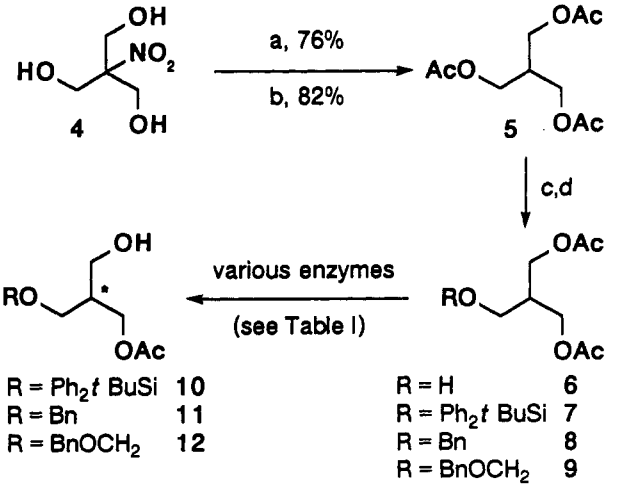
One of the most widely used approaches to the synthesis of enantiomerically pure compounds employs small functionalized optically active molecules usually referred to as "chiral building blocks". Unfortunately, the number of such compounds directly available from natural sources is limited, and therefore continuous efforts are currently made in order to increase the so-called "chirality pool". In the course of a research program directed toward the preparation of new chiral building blocks,[2] we were particularly attracted by the structure of the C_{3v} symmetric tris(hydroxymethyl)methane (**1**, Chart I). This molecule, thanks to the different transformations feasible starting from an alcoholic function, can be viewed as a potential starting material for a wide range of chiral synthetic targets. Obviously, this goal can be successfully achieved only if there is a way to distinguish between the three equivalent hydroxymethyl groups or, in other words, to prepare an "asymmetrized tris(hydroxymethyl)methane" like, for example, **2** where $R^1 \neq R^2 \neq R^3$.

We have previously reported in a preliminary form an efficient method for the preparation of synthetic equivalents of **2** and of the related aldehydes **3** through enantioselective enzyme-catalyzed hydrolysis of prochiral diacetates[1a,b] and have also demonstrated the peculiar stereochemical properties[1c] and the synthetic utility[3] of these new chiral building blocks.[4,5] Now we present a full account on our studies in this area, as well as more experimental details on the preparation of a series of compounds **2** ("asymmetrized tris(hydroxymethyl)methane", "THYM*") and **3** ("asymmetrized bis(hydroxymethyl)-acetaldehyde", "BHYMA*").

Chart I



Scheme I[a]



[a] Key: (a) Ac_2O, Et_3N, DMAP; (b) nBu$_3$SnH, AIBN; (c) PPL, pH 7; (d) for **7**, Ph$_2$*t*BuSiCl, imidazole, DMF, 75% from **5**; for **8**, BnBr, NaH, DMF, 56% from **5**; for **9**, $BnOCH_2Cl$, $EtN(iPr)_2$, 76% from **5**.

Attempted Preparation of THYM* 2 through Enzymatic Hydrolysis of 2-(Alkoxymethyl)-1,3-diacetoxypropanes. At first we reasoned that the simplest approach to **2** would have been the one starting from triacetate **5** (Scheme I), which is in turn prepared in two steps from commercially available tris(hydroxymethyl)-nitromethane (**4**).[6]

In order to differentiate the three equivalent groups we needed the following: (a) a substrate selectivity allowing deprotection of just one hydroxyl group in **5** and (b) an enantioselective transformation, with recognition of the

(1) Part of this work was already reported in preliminary form: (a) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 2697. (b) *Tetrahedron: Asymmetry* **1990**, *1*, 721; (c) *Tetrahedron Lett.* **1990**, *31*, 6421.

(2) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5507; **1989**, *30*, 5511.

(3) Guanti, G.; Banfi, L.; Ghiron, C.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 267.

(4) For another chemoenzymatic approach to the same building blocks through porcine pancreatic lipase catalyzed asymmetrization of ethyl 3-acetoxy-2-(acetoxymethyl)propionate see: Ehrler, L.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 379.

(5) For a possible nonenzymatic route to **2**, see: Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527.

(6) Latour, S.; Wuest, J. D. *Synthesis* **1987**, 742.

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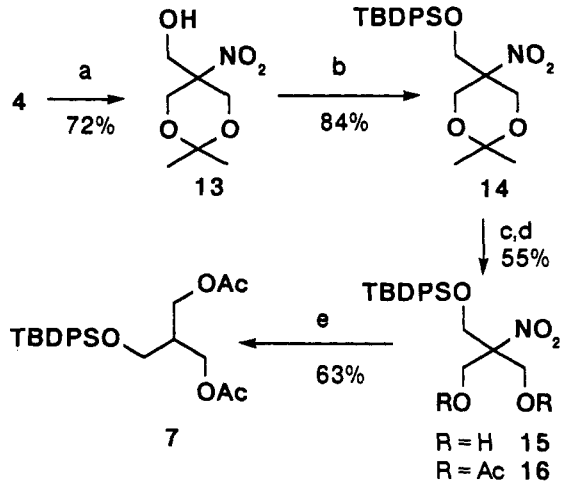
Scheme II[a]



[a] Key: (a) see ref 9; (b) $Ph_2tBuSiCl$, imidazole, DMF; (c) *p*TSA, MeOH; (d) Ac_2O, Et_3N, DMAP; (e) nBu_3SnH, AIBN.

Table I. Enzyme-Catalyzed Monohydrolysis of 2-(Alkoxymethyl)-1,3-diacetoxypropanes

entry	diacetate	enzyme[a]	yield,[b] (%)	ee,[c] (%)
1	7	PPL	no reaction	
2	7	PLE	no reaction	
3	8	PPL	33	11
4	8	acetyl cholinesterase	20	≈0
5	9	PPL	29	7
6	9	PLE	24	2
7	9	CCL	33	13
8	9	acetyl cholinesterase	17	11

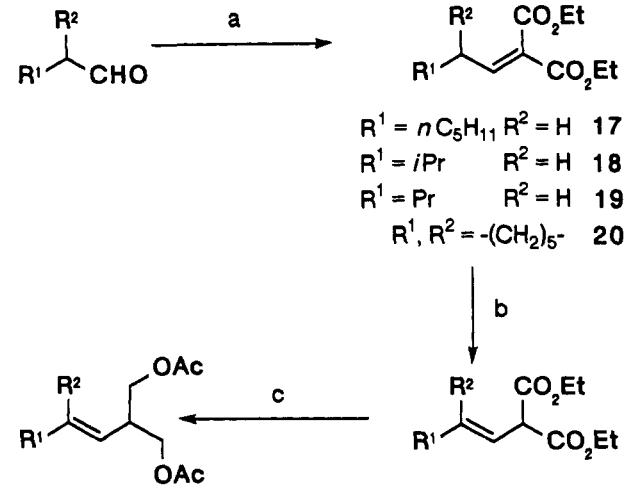
[a] PPL = pig pancreas lipase; PLE = pig liver esterase; CCL = *Candida cylindracea* lipase. [b] Isolated yields. [c] Absolute configuration not determined.

two remaining enantiotopic acetoxymethyl groups in **7–9**. Although the accomplishment of these two purposes by conventional methods was expected to be very difficult, we hoped to succeed with the aid of enzymes.[7]

Actually, enzymes worked well in solving the first problem; conversion of triacetate **5** into diacetate **6** proceeded with high substrate selectivity under the catalysis of pig pancreatic lipase (PPL) to give after reprotection of the free hydroxyl group, compounds **7–9** in good yields.[8] The silyl-protected diacetate **7** was also prepared through an alternative pathway, based on the selective blocking of only two of the hydroxyl groups in **4** through formation of an isopropylidene derivative (Scheme II).

Unfortunately, the monohydrolysis of these diacetates was by far less rewarding. As shown in Table I, while silyl-protected diacetate **7** proved to be unreactive in the presence of both PPL and PLE (pig liver esterase), the other two prochiral compounds afforded only disappointing yields and poor enantiomeric excesses with four different enzymes. While many other enzymes and protecting groups could have been screened, these unsatisfactory results led us to think that this approach, although simplest in principle, was not most likely the best one.[10]

Scheme III[a]



R¹ = nC_5H_{11} R² = H **25**
R¹ = *i*Pr R² = H **26**
R¹ = Pr R² = H **27**
R¹, R² = -$(CH_2)_5$- **28**

R¹ = nC_5H_{11} R² = H **21**
R¹ = *i*Pr R² = H **22**
R¹ = Pr R² = H **23**
R¹, R² = -$(CH_2)_5$- **24**

[a] Key: (a) diethyl malonate, piperidinium acetate, benzene, 58% (**17**), 89% (**18**), 55% (**19**), 92% (**20**); (b) LDA, THF–HMPA, –78 °C, then H^+, 72% (**21**) or NaH, THF, then H^+, 70% (**22**), 46% (**23**), 50% (**24**); (c) $LiAlH_4$, Et_2O; then Et_3N, DMAP, Ac_2O, 83% (**25**), 40% (**27**), 59% (**28**) or Ac_2O, pyridine, 68% (**26**).

Probably the CH_2OAc and CH_2OR groups are too similar to be sufficiently differentiated by the enzyme. Therefore, we turned our efforts to other 1,3-diacetoxypropanes substituted at position 2 with a group synthetically equivalent to the CH_2OR moiety and better suited for efficient enantioselective monohydrolysis. A careful examination of the literature data[11] on the enzymatic hydrolysis of 2-substituted 1,3-diacetoxypropanes suggested that, at least in the case of PPL, the presence of a π system near the prochiral center could have a beneficial effect on the enantioselectivity.[12] Since a double bond can be easily broken through ozonolysis, the $R^1R^2C{=}CH-$ substituent can be regarded as synthetically equivalent to a formyl or, upon reduction, to a hydroxymethyl group.

Therefore, we decided to synthesize a series of 2-alkenyl-1,3-diacetoxypropanes (Scheme III) and to study their behavior in enzyme-catalyzed monohydrolysis.

Preparation and Asymmetrization of 2(*E*)-Alkenyl-1,3-diacetoxypropanes. The preparation of **25–28** is described in Scheme III and included a Knoevenagel

(7) Recent reviews on hydrolytic enzymes in organic synthesis: (a) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. (b) Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (c) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (d) Crout, D. H. G.; Christen, M. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Berlin, 1989; Vol. 5, p 1.

(8) We obtained better overall yields when crude **6** was directly protected without purification.

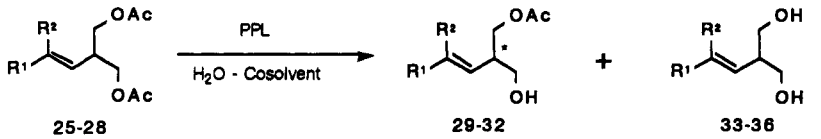
(9) Linden, G. B.; Gold, M. H. *J. Org. Chem.* **1956**, *21*, 1175.

(10) These unsatisfactory results are in line with those obtained by Seebach[4] with 2-methyl-2-[(benzyloxy)methyl]-1,3-diacetoxypropanes.

(11) For preparations of asymmetrized 2-monosubstituted 1,3-propanediols via enzymatic methods see: ref 4 and (a) Wang, Y. F.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 4999. (b) Ramos Tombo, G. M.; Schaer, H. P.; Fernandez, I.; Busquets, X.; Ghisalba, O. *Tetrahedron Lett.* **1986**, *27*, 5707. (c) Kerscher, V.; Kreiser, W. *Tetrahedron Lett.* **1987**, *28*, 531. (d) Breitgoff, D.; Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1523. (e) Eberle, M.; Egli, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1. (f) Terao, Y.; Murata, M.; Achiwa, K.; Nishio, T.; Akamatsu, M.; Kamimura, M. *Tetrahedron Lett.* **1988**, *29*, 5173. (g) Tsuji, K.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 6189. (h) Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. (i) Xie, Z. F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1638. (j) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1989**, 957. (k) Barnett, C. J.; Wilson, T. M. *Tetrahedron Lett.* **1989**, *30*, 6291. (l) Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081.

(12) For example, 1,3-diacetoxy-2-phenylpropane gave 92% ee in PPL-catalyzed monohydrolysis[11l] while 1,3-diacetoxy-2-cyclohexylpropane afforded only 60% ee;[11b] moreover, 1,3-diacetoxy-2-benzylpropane gave 61% ee compared to virtually no enantioselection for 1,3-diacetoxy-2-cyclohexylmethylpropane (this work and ref 11b).

Table II. PPL-Catalyzed Hydrolysis of 2-Alkenyl-1,3-diacetoxypropanes 25–28[a]



25-28 29-32 33-36

entry	substrate	product	diol	solvent	initial/final rate	% monoacetate[b]	isolated yield (%)	$[\alpha]_D$	ee (%)	configuration
1	**25**	**29**	**33**	H_2O	1.49	62	49	−17.3°	84	*S*
2	**25**	**29**	**33**	H_2O/THF (85:15)	1.85	69	62	−18.6°	86	*S*
3	**25**	**29**	**33**	H_2O/*t*BuOH (9:1)	2.22	66	59	−19.8°	93	*S*
4	**25**	**29**	**33**	H_2O/*i*Pr_2O (7:3)	4.16	60	42	−16.0°	73	*S*
5	**25**	**29**	**33**	H_2O/*i*Pr_2O (85:15)	2.17	66	63	−21.8°	95	*S*
6	**26**	**30**	**34**	H_2O	5.26	78	70	−23.2°	90	*S*
7	**26**	**30**	**34**	H_2O/*t*BuOH (9:1)	25	85	71	−23.2°	88	*S*
8	**26**	**30**	**34**	H_2O/*i*Pr_2O (85:15)	20	84	75	−25.3°	97	*S*
9	**27**	**31**	**35**	H_2O/*i*Pr_2O (85:15)	3.13	57	46	−25.1°	94	*S*
10	**28**	**32**	**36**	H_2O/*i*Pr_2O (85:15)	1.72	33	29	−19.0°	67	*S*

[a] All reactions were stopped at ≈50% conversion (based on acetyl group hydrolysis). For reaction conditions and analytical methods see the Experimental Section. [b] Molar percentage of monoacetate on the total recovery of monoacetate, diacetate, and diol.

condensation between diethyl malonate and various aldehydes,[13,14] followed by deconjugation of the resulting alkylidenemalonates **17–20**.

This isomerization was initially carried out on substrate **17** following the conditions reported by Takeda et al.,[15] which involve dienolate formation with LDA in THF–HMPA followed by kinetic quenching with acids. As expected, only the *E* deconjugated product was formed in this reaction. Although the yields were good, the use of toxic and nonvolatile HMPA caused some problems in reaction scale-up.[16] Moreover, when we tried to apply the same procedure to the branched malonate **18**, we always obtained a mixture of conjugate and deconjugated isomers **18** and **22**. A similar result was obtained even when a large excess of LDA for long reaction times was used. Moreover, the **22**/**18** ratio depended on quenching conditions.[17] These data suggest that this unexpected behavior was not due to incomplete metalation, but most likely to a lower preference, under kinetic control, for α-attack in the reprotonation step. Although kinetic reprotonation of ester, ketone, or acid dienolates in α position is usually the rule, some notable exceptions are known in the literature.[18]

So we turned to an alternative method involving deprotonation with sodium hydride in tetrahydrofuran followed by reprotonation with aqueous boric acid at 0 °C.[19] Although the yields were somewhat lower, we found in all cases complete and highly stereoselective deconjugation. Moreover, the reaction conditions and workup were better suited for large-scale preparation. The different behavior from Takeda's method can be due to the different counterion or to the absence, in this case, of HMPA. Reduction with $LiAlH_4$ of the resulting alkenylmalonates followed by acetylation furnished the desired diacetates **25–28** in good overall yields. It is worth noting that in the case of **26** all the reagents employed in this reaction sequence are inexpensive and both **26** and all its synthetic intermediates can be easily purified through distillation, thus allowing an easier scale-up (we prepared up to 0.3 mol of **26**).

Diacetates **25–28** were then subjected to pig pancreatic lipase (PPL) catalyzed monohydrolyses under various conditions. Table II shows the results obtained, displaying not only the enantiomeric excesses, but also other relevant features, like the percentage of monoacetate on the overall recovery of monoacetate + diacetate + diol and the initial rate/final rate ratio. These two data are closely related to the substrate selectivity and thence to the chemical yield. All the reactions were stopped at 50% conversion (based on hydrolysis of initial acetyl groups) in order to get comparable results from the various substrates. Table II clearly indicates that all three substrates containing an *E* disubstituted double bond can be hydrolyzed with excellent enantioselection (94–97%). Although acceptable results were obtained using water as reaction medium (entries 1 and 6), a significant improvement was gained by adding appropriate organic cosolvents like THF, *t*BuOH, and diisopropyl ether.[20] The best cosolvent turned out to be diisopropyl ether. When used in 15:85 ratio with water it allowed a clear improvement in both yield and enantiomeric excess (compare entry 1 with entry 5 and entry 6 with entry 8). Among the three diacetates, the branched derivative **26** proved to be superior to the straight-chain analogues **25** and **27**; a slight increase in the enantioselection was accompanied by a marked improvement in substrate selectivity and yield, as well as in the initial to final rate ratio. Actually (entry 8) the reaction proceeded with high substrate selectivity, almost stopping at 50% conversion.

(13) Cope, A. C.; Hofmann, C. M.; Wyckoff, C.; Hardenberg, E. *J. Am. Chem. Soc.* **1941**, *63*, 3452.

(14) In some cases (**17–19**) the alkylidene malonates obtained under the condition described in ref 13 contained 2–25% of the deconjugate compounds **21–23**.

(15) Tsuboi, S.; Muranaka, K.; Sakai, T.; Takeda, A. *J. Org. Chem.* **1986**, *51*, 4944.

(16) In the absence of HMPA, which is known to form a complex with LDA, thus limiting its nucleophilicity, the yields were lower and, most important, product **21** was contaminated by unseparable byproducts, probably derived by 1,4-addition of LDA to **17**. These byproducts, after subsequent $LiAlH_4$ reduction and acetylation, led to the formation of the saturated diacetate **37** (Scheme IV), whose separation from **25** proved to be nearly impossible.

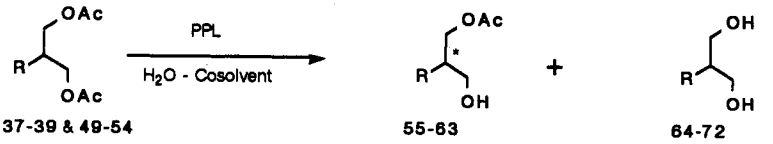
(17) Under the best conditions (quenching at −78 °C) we obtained a 3:1 ratio of **22** and **18**.

(18) Ballester, P.; Costa, A.; Garcia-Raso, A.; Mestres, R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 21. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1981**, *46*, 2439. Pitzele, B. S.; Baran, J. S.; Steinman, D. H. *Tetrahedron* **1976**, *32*, 1347. Thebtaranonth, Y.; Yenjai, C. *Tetrahedron Lett.* **1985**, *26*, 4097. Savu, P. M.; Katzenellenbogen, J. A. *J. Org. Chem.* **1981**, *46*, 239 and references cited therein.

(19) Steinbeck, K.; Osterwinter, B. *Tetrahedron Lett.* **1979**, 861.

(20) The use of THF and diisopropyl ether as cosolvents in PPL-catalyzed reactions was already reported (refs 11d and 11c, respectively); *t*BuOH was shown by us to improve dramatically the selectivity in a PLE-catalyzed hydrolysis (Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1986**, *27*, 4639). For the use of these and other cosolvents in enzyme-catalyzed hydrolyses see also ref 7b.

Table III. PPL-Catalyzed Hydrolysis of 2-Substituted 1,3-Diacetoxypropanes 37–39 and 49–54[a]

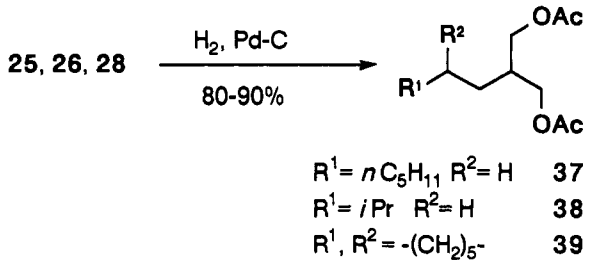


37-39 & 49-54 55-63 64-72

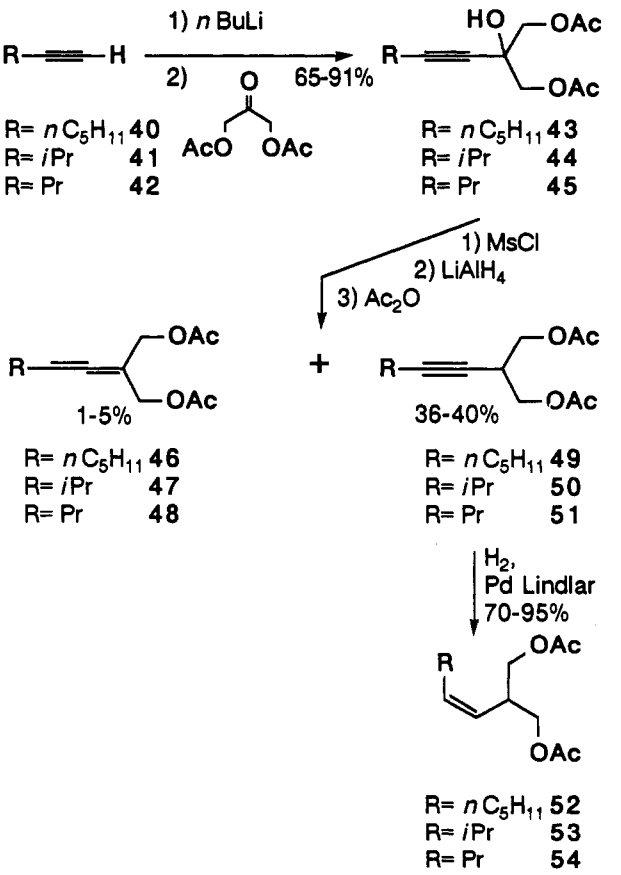
entry	substrate	product	diol	solvent	initial/final rate	% monoacetate[b]	isolated yield (%)	$[\alpha]_D$	ee (%)	configuration
1	37	55	64	H_2O/iPr_2O (85:15)	1.61	65	56	−7.87°	70	*S*
2	38	56	65	H_2O/iPr_2O (85:15)	2.00	59	47	−8.56°	72	*S*
3	39	57	66	H_2O/iPr_2O (85:15)	1.00	50	45	+0.1°	2	nd
4	49	58	67	H_2O	1.52	62	57	−10.2°	78	*S*
5	49	58	67	H_2O/tBuOH (9:1)	1.89	67	61	−10.8°	82	*S*
6	49	58	67	H_2O/iPr_2O (85:15)	1.27	56	50	−10.2°	80	*S*
7	50	59	68	H_2O	2.70	79	67	−10.0°	82	*S*
8	50	59	68	H_2O/tBuOH (9:1)	5.00	82	71	−10.4°	88	*S*
9	50	59	68	H_2O/iPr_2O (85:15)	4.17	80	65	−10.4°	85	*S*
10	51	60	69	H_2O/tBuOH (9:1)	4.50	79	62	−9.9°	83	*S*
11	51	60	69	H_2O/iPr_2O (85:15)	1.66	62	50	−9.3°	80	*S*
12	52	61	70	H_2O	1.52	48	43	+13.3°	50	*R*
13	52	61	70	H_2O/tBuOH (9:1)	2.38	48	44	+14.4°	55	*R*
14	52	61	70	H_2O/iPr_2O (85:15)	1.47	40	31	+14.5°	53	*R*
15	53	62	71	H_2O	1.79	37	25	+4.7°	21	*R*
16	53	62	71	H_2O/iPr_2O (85:15)	1.00	32	20	+2.2°	15	*R*
17	54	63	72	H_2O/iPr_2O (85:15)	1.25	28	25	+12.0°	42	*R*

[a] All reactions were stopped at ≈50% conversion (based on acetyl group hydrolysis). For reaction conditions and analytical methods see the Experimental Section. [b] Molar percentage of monoacetate on the total recovery of monoacetate, diacetate, and diol.

Scheme IV



Scheme V



Therefore, taking into account that **26** is more efficiently prepared than the other diacetates because of the better yields and easier workup of the Knoevenagel condensation, *we recommend **26** as the substrate of choice for the obtainment of asymmetrized tris(hydroxymethyl)methane.*

In contrast with the excellent enantioselectivities found for the (*E*)-alkenyl derivatives, the trisubstituted diacetate **28** reacted with poor substrate selectivity (and hence unsatisfactory yield) and only moderate enantioselectivity.

Although the overall findings seem to support our first feeling on the beneficial effect of a π system near the prochiral center,[21] this last result shows that the type of substitution on the double bond can also have a great impact on the enantioselection.

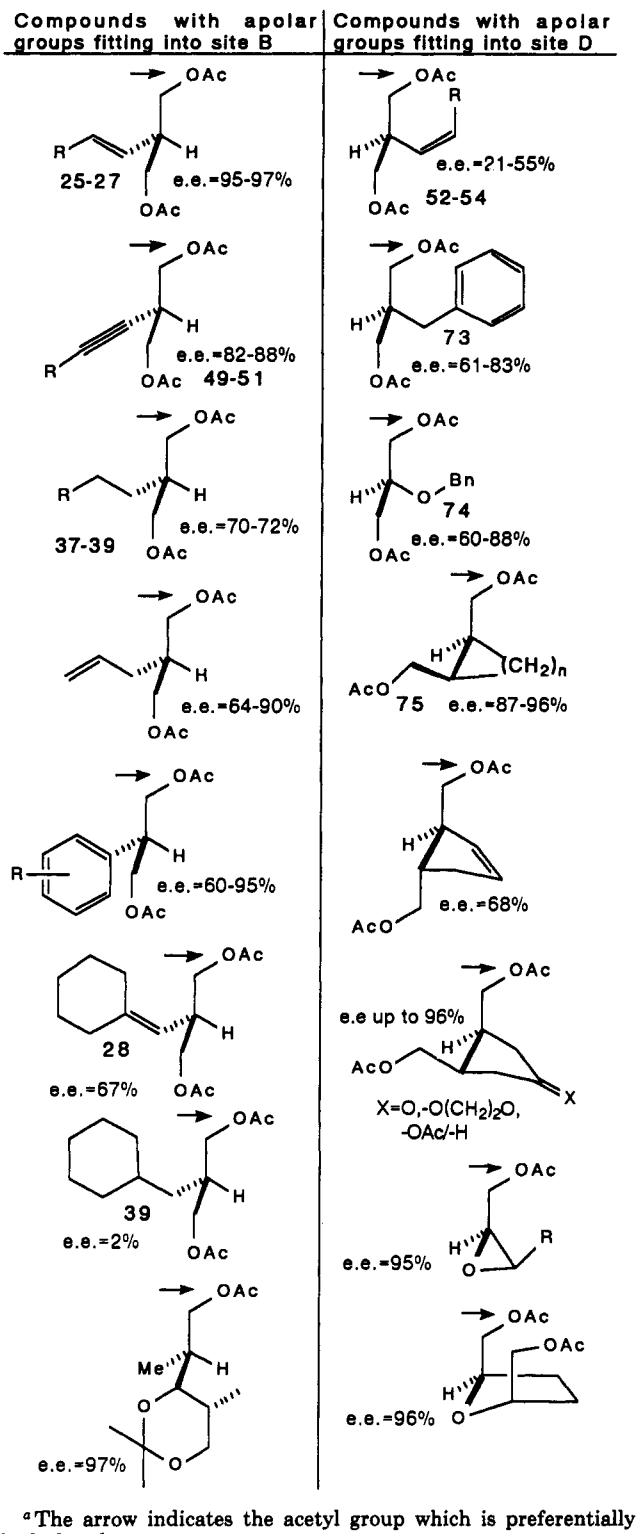
Therefore, in order to better uncover the real scope of PPL-catalyzed hydrolysis of these substrates, we decided to study in more details the effect of the unsaturation on the enantioselectivity, and for this purpose, we synthesized a series of 1,3-diacetoxypropanes bearing saturated alkyl, (*Z*)-alkenyl, or alkynyl substituents in position 2 and compared their monohydrolyses.

Preparation and Asymmetrization of 2-Alkyl-, 2-Alkynyl-, and 2-(*Z*)-Alkenyl-1,3-diacetoxypropanes. The saturated diacetates **37–39** were easily obtained through hydrogenation of compounds **25**, **26**, and **28** (Scheme IV). For the preparation of 2-alkynyl derivatives **49–51** (Scheme V) we used as starting material diacetoxyacetone,[22] which, by reaction with the lithium deriva-

(21) For other cases of influence of a π system on enzyme-catalyzed reactions see: (a) Nakada, M.; Kobayashi, S.; Ohno, M.; Iwasaki, S.; Okuda, S. *Tetrahedron Lett.* **1988**, *29*, 3951. (b) Lutz, D.; Güldner, A.; Thums, R.; Schreier, P. *Tetrahedron: Asymmetry* **1990**, *1*, 783. (c) Oberhauser, T.; Faber, K.; Griengl, H. *Tetrahedron* **1989**, *45*, 1679.

(22) Bentley, P. H.; McCrae, W. *J. Org. Chem.* **1970**, *35*, 2082.

Chart II[a]



[a] The arrow indicates the acetyl group which is preferentially hydrolyzed.

tives of alkynes **40–42**, gave in good to excellent yields[23] the tertiary alcohols **43–45**. Deoxygenation was carried out in moderate yields through $LiAlH_4$ reduction of the corresponding mesylates, followed by acetylation of the resulting diols. During this reduction we also obtained variable amounts of the corresponding allenes which were chromatographically separated from the alkynes at the diacetate stage. Finally, Lindlar hydrogenation of the alkynes **49–51** furnished stereoselectively the (*Z*)-alkenyl derivatives **52–54**.[24]

The results of PPL-catalyzed monohydrolysis of these substrates are shown in Table III. The first three entries refer to the saturated compounds and indicate that saturation provoked a marked decrease in enantioselection by comparison with the corresponding 2(*E*)-alkenyl diacetates. In the case of cyclohexylmethyl derivative **39** the reaction was virtually nonselective. On the other hand, the hydrolysis of alkynyl derivatives, reported in entries 4–11, reveals that the presence of a triple bond is still capable of bringing about an acceptable asymmetric induction, although to a lesser extent than the *E* double bond. As in the (*E*)-alkenyl series, the best results both in terms of substrate selectivity (and yield) and enantioselection were obtained for the branched substrate **50**. In this series *tert*-butyl alcohol was found to be slightly superior to iPr_2O as the organic cosolvent.

However, the most striking and unexpected outcome derived from hydrolysis of the 2(*Z*)-alkenyl diacetates. As shown in entries 12–17, *a net reversal of enantioselectivity was observed*! This reversal was also accompanied by a decrease in substrate selectivity, initial to final rate ratio, and yield. To our knowledge this is the first example of such a dramatic effect on the enantioselectivity in an enzyme-catalyzed hydrolysis, caused merely by inversion of double-bond configuration. This finding is somehow in line with the low selectivity in the hydrolysis of diacetate **28** (Table II), where the double bond bears substituents both in cis and trans position.

Proposal of an Empirical Model for the Interpretation of Stereochemical Outcome. Since crude PPL is known to contain different enzymes and scarce information is available on its active site, rationalization of these results is not simple. However, a comparison with other literature data is possible and a summary of so far performed PPL-catalyzed monohydrolysis of acetylated primary alcohols having an α prochiral or chiral center is reported in Chart II.[27]

Examination of the results indicates that both polar and steric factors appear to affect the stereochemical outcome. On the basis of these data we have tried to design a simple empirical model where both of these factors are taken into account.[28] Chart III shows as an example the application

(23) Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637. Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723.

(24) Compound **52** was also prepared by us in an alternative, less efficient, way through deconjugative hydroxyalkylation of (*E*)-ethyl 2-nonenoate[25] (1. LDA; 2. monomeric HCHO, THF, −78 °C, 17% yield, 85:15 *Z*:*E* ratio[26]) followed by $LiAlH_4$ reduction and acetylation (54%).

(25) Villieras, J.; Rambaud, M. *Synthesis* **1983**, 301.

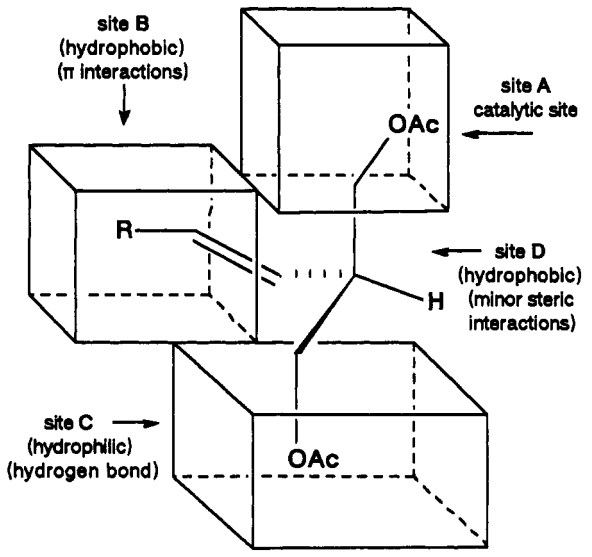
(26) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. Ikeda, Y.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5181.

(27) For references see ref 4, 11j,l. The comparison among ee should be taken as merely indicative, since the reactions were performed under different experimental conditions and at different degrees of conversion.

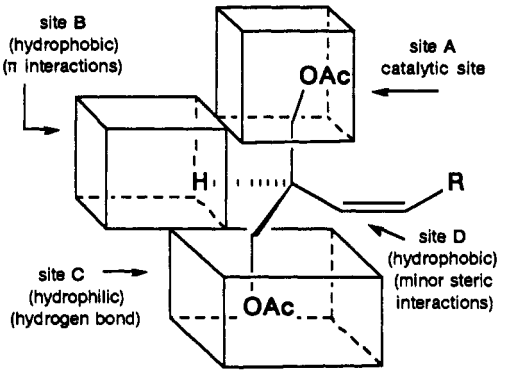
(28) An alternative empirical model where only polar factors are considered has recently been proposed by Seebach.[4] For other empirical models regarding other enzymes see: Pig liver esterase (a) Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501. (b) Ohno, M. In *Enzymes in Organic Synthesis*; Clark, R., Porter, S., Eds.; Pitman: London, 1985. (c) Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047. (d) Bjorkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron Lett.* **1985**, *41*, 1347. (e) Zemlicka, J.; Craine, L. E.; Heeg, M. J.; Oliver, J. P. *J. Org. Chem.* **1988**, *53*, 937. (f) Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946. (g) Kloosterman, M.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1990**, *55*, 5878. *Pseudomonas fluorescens* lipase (h) Xie, Z. F.; Nakamura, I.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 966. Lipase A6 (i) Itoh, T.; Kuroda, K.; Tomosada, M.; Takagi, Y. *J. Org. Chem.* **1991**, *56*, 797. *Candida cylindracea* lipase ref 21c. Crude Pancreatic Extract ref 21b.

Chart III

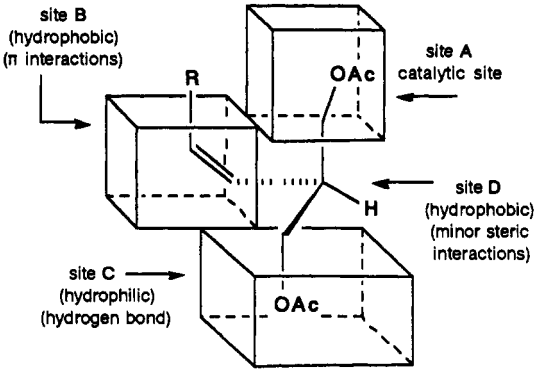
Preferred disposition for 2-(*E*)-alkenyl-1,3-diacetoxypropanes



Preferred disposition for 2-(*Z*)-alkenyl-1,3-diacetoxypropanes



Unfavoured disposition for 2-(*Z*)-alkenyl-1,3-diacetoxypropanes



of this model for 2-alkenyl-1,3-diacetoxypropanes. According to our proposal, the active site of the enzyme should contain three additional pockets besides the catalytic one (A). One of these regions is hydrophilic (C) and is prone to accept the other acetoxy group as well as other polar groups present near the chiral or prochiral center. Of the two remaining sites, which generally accommodate apolar substituents, one (D) is less structurally and sterically demanding and is able to accept with scarce restrictions different acyclic or cyclic chains or substituents, whereas the other (B) is more selective and better accepts only suitably tailored apolar chains, especially when they bear π bonds. The best fitting of the various parts of the molecule into these three sites will determine which CH_2OAc (*pro-R* or *pro-S* for prochiral substrates, *S* or *R* for meso compounds or racemic mixtures) will be hydrolyzed preferentially thus being responsible for the stereochemical outcome. From the data in Chart II it appears that saturated (linear or γ-branched) and, better yet, unsaturated (allylic, (*E*)-alkenyl, alkynyl, and aromatic) substituents fit in site B while cyclic, (*Z*)-alkenyl, benzyl, and benzyloxy groups prefer to fit in site D. This fact seems to support a general preference of apolar substituents (especially when bearing an unsaturation) for site B, unless they present particular steric constraints that make it difficult to fit into this pocket. These constraints can be as follows: (a) a substituent in β position fixed in a cis or cislike position (this is the case of (*Z*)-alkenyl-substituted compounds **52–54** or cyclic compounds like for example **75**[4]) or (b) a double substitution at the β-carbon (see for example the inversion of configuration for 2-benzyl-1,3-diacetoxypropane **73**[11j] and the diminished selectivity for compounds **28** and **39**).[29] The preference of apolar substituents for smaller site B when their size allows them to enter it is in accord with the general principle that the best hydrophobic interactions occurs when the entering species completely fills the hydrophobic pocket.[28f]

Obviously, further proofs are needed to confirm the validity of this model, and for this purpose we are preparing other suitably 2-substituted 1,3-diacetoxypropanes in order to test the generality of the above described proposal.

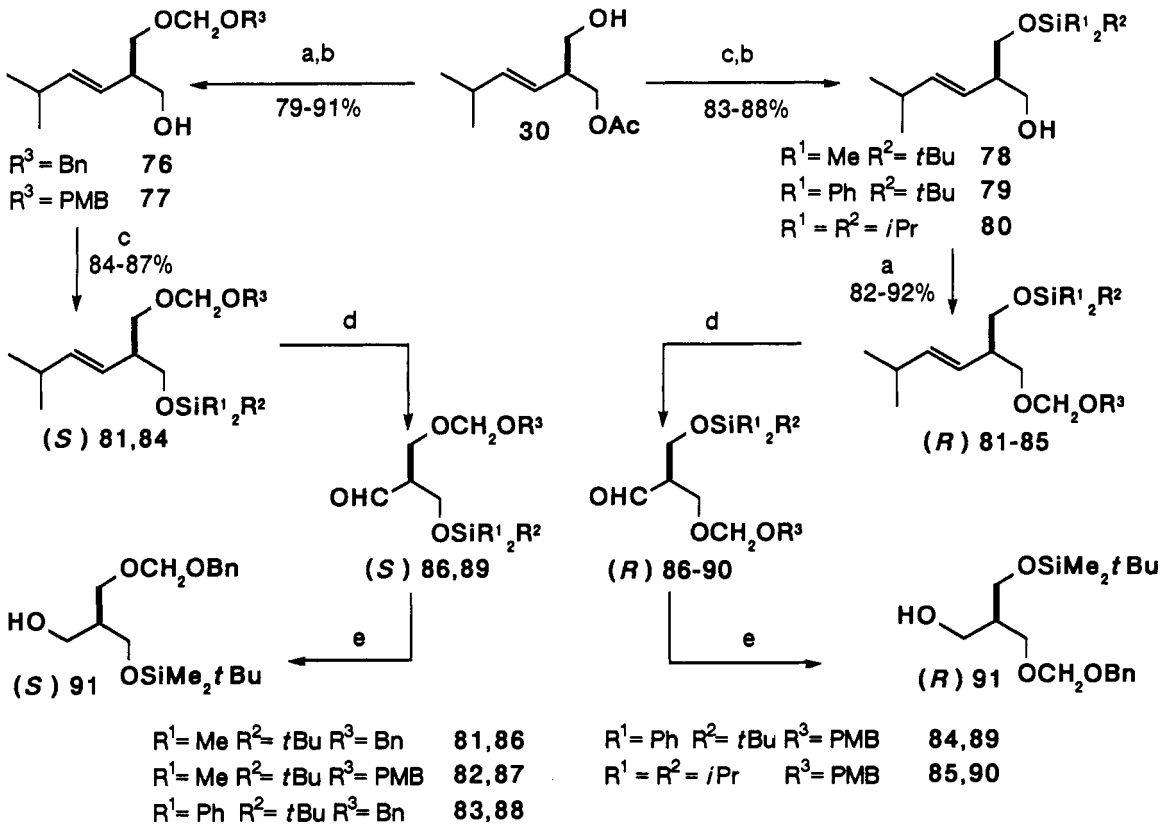
From a synthetical point of view we may conclude that PPL-catalyzed monohydrolysis is a convenient method for direct obtainment of asymmetrized 2(*E*)-alkenyl- and 2-alkynyl-1,3-propanediols. Although 2-alkyl and 2-(*Z*)-alkenyl compounds seem to be not directly accessible in satisfactory ee's, it should be pointed out that they can be indeed easily prepared through controlled hydrogenation of the triple bond (for the *Z* compounds) or through normal hydrogenation of the *E* double bond (for saturated derivatives).

It is important to stress that all the reactions reported in Tables I–III were stopped at 50% conversion in order to get comparable results among the various substrates. However, an improvement of the ee can be in principle gained (at the expense of the chemical yield) by carrying on the hydrolyses to a higher degree of conversion, as well stated by Sih et al.[7b]

We also considered the possibility to asymmetrize 2-substituted 1,3-propanediols through enzyme-catalyzed

(29) The case of 2-(benzyloxy)-1,3-diacetoxypropane **74** is more difficult to interpret only on a steric basis. A possible explanation is that the BzlO group is too polar to be accepted in site B, which requires only completely unpolar substituents; thus, it must accommodate in site D.

Scheme VI[a]

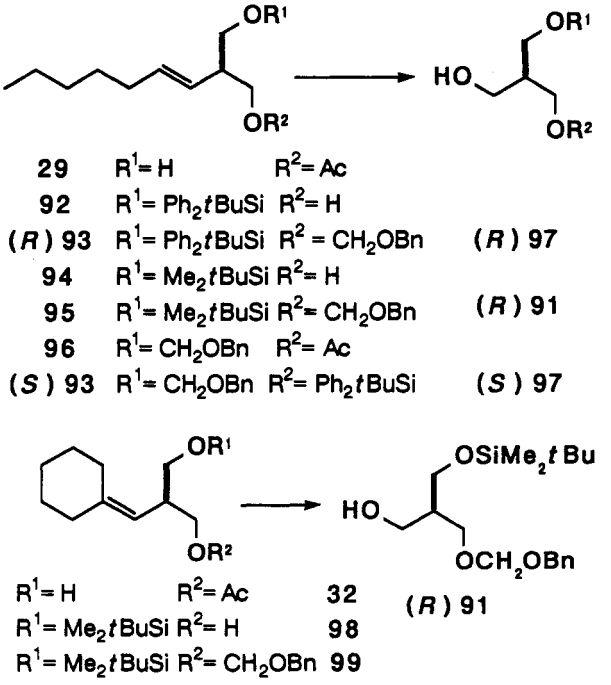


[a] Key: (a) R^3OCH_2Cl, $EtN(iPr)_2$, CH_2Cl_2; (b) KOH, MeOH; (c) $R^2R^1{}_2SiCl$, imidazole, DMF or $R^2R^1{}_2SiOTf$, 2,6-lutidine, CH_2Cl_2; (d) O_3, $MeOH-CH_2Cl_2$; (e) $NaBH_4$, MeOH.

monoacetylation in organic solvents. This strategy has been already applied to this kind of substrates in some particular cases.[11b,f-h,j,k] We obtained moderately good results in the monoacetylation of diol **34** catalyzed by lipase from Pseudomonas fluorescens (SAM-II); when the reaction was carried out in dry $CHCl_3$ in the presence of vinyl acetate[11h,30] we obtained a 50% yield of monoacetate **30** with an ee of 75%. As expected, in this case the major enantiomer was found to be *R*, and so PPL-catalyzed hydrolysis and SAM-II-catalyzed acetylation can be viewed as complementary. However, due to the enantiodivergency property of these monoacetates (vide infra) this complementary asymmetrization is not really necessary and so we recommend the use of the more efficient PPL-catalyzed monohydrolysis of the diacetate **26**.

We have also carried out a preliminary study on asymmetrization of allene **46**. PPL-catalyzed hydrolysis was found to be slightly faster in this case than for the alkynyl or (*E*)-alkenyl substrates. The reaction in water, stopped at 50% conversion, gave in good isolated yield (61%) and in 78% ee ($[\alpha]_D = +3.29°$) an optically active monoacetate whose absolute configuration was not determined.[31] This promising result suggests that this could be a simple and efficient approach to chiral allenyl derivatives whose preparation is usually troublesome.[32] Obviously the development of a more efficient preparation of **46** is needed. Work directed toward this goal is in progress.

Scheme VII



Enantiodivergent Transformation of Monoacetate 30 into Variously Protected THYM* and BHYMA* Chiral Building Blocks. Having in hand an efficient method for the obtainment of monoacetate **30** in high ee, we then performed its conversion into various synthetic equivalents of asymmetrized tris(hydroxymethyl)methane

(30) Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K. E.; Schneider, M. P. *Tetrahedron Lett.* **1989**, *30*, 1793 and references cited therein.

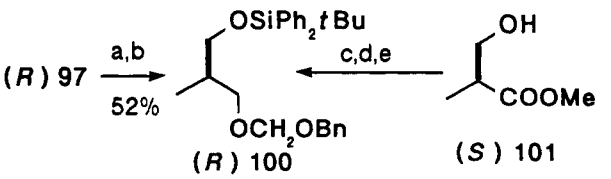
(31) The use of hydrolytic enzymes in preparing optically active allenes was already reported: (a) Ramaswamy, S.; Hui, R. A. H. F.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1545. (b) Gill, G.; Ferre, E.; Meou, A.; Le Petit, J.; Triantaphylides, C. *Tetrahedron Lett.* **1987**, *28*, 1647. These two reports, however, concern the resolution of racemic substrates.

(32) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726 and references cited therein.

(THYM*) or asymmetrized bis(hydroxymethyl)acetaldehyde (BHYMA*).[33] Scheme VI illustrates the high yield conversion of **30** into a series of diprotected 2-alkenyl-1,3-propanediols **81–85**.[34] *It is worth noting that it is possible to prepare both enantiomers of a given compound simply by reversing the order of protective group introduction.* As an example we report the preparation in comparable yields of both (*R*)- and (*S*)-**81** and -**84**. Therefore, we can say that monoacetate **30** is an *enantiodivergent chiral building block*.[36] These alkenyl derivatives were smoothly ozonolyzed to afford the BHYMA* equivalents **86–90**, which can be in turn reduced to the corresponding THYM* equivalents, like, for example, **91**. The yield of the ozonolysis was not determined, since we always preferred to use the crude aldehydes **86–90** without purification. However, from the overall yield after $NaBH_4$ reduction or condensation of these aldehydes,[1c,3] we may infer a yield of the ozonolysis step of at least 95%.[34]

In choosing the type of protecting group to be introduced, we took into account our projection to use BHYMA* equivalents in diastereoselective condensations with various C-nucleophiles. The successful achievement of this goal[1c,3,37] required that the two protecting groups in aldehydes **86–90** were endowed with different chelating capabilities.[38] Thus, we chose a series of silyl protecting groups which are expected to be "non-chelating"[38] and two alkoxymethyl groups, $BnOCH_2$ and [(*p*-methoxybenzyl)oxy]methyl ($PMBOCH_2$)[35] groups, which, on the contrary, should be able to form chelates.[38] Other potential "chelating" protecting groups could be the benzyl ethers. However, when we tried to protect in this way alcohols **30**, **78**, and **79** under the usual basic conditions (NaH, DMF, benzyl bromide, or *p*-methoxybenzyl chloride), we detected a variable percentage of racemization, most likely due to scrambling of the acetyl or silyl protecting group from one OH to the other. Racemization was also detected after treatment of **78** with NaH in DMF for 1 h. On the contrary, the reaction conditions used for all the protecting and deprotecting steps described in Scheme VI did not affect at all the stereochemical integrity of the substrates.[39]

Scheme VIII[a]



[a] Key: (a) TsCl, Et_3N, DMAP, CH_2Cl_2; (b) $NaBH_4$, DMSO; (c) $Ph_2tBuSiCl$; (d) $LiAlH_4$;[41] (e) $BnOCH_2Cl$, $EtN(iPr)_2$, 62%.

Following a similar procedure, the linear monoacetate **29** was also converted into THYM* equivalents (*R*)-**91**, and (*R*)- or (*S*)-**97** (Scheme VII).

Determination of Absolute Configuration. Alkenyl, alkynyl, and saturated monoacetates bearing the same carbon chain were relatively correlated to each other through hydrogenation of the first two to give the saturated monoacetates and by measuring their $[\alpha]_D$. During these hydrogenations it is important to avoid unnecessary long reaction times and/or high catalyst quantities in order to prevent small percentages of racemization. The (*E*)-alkenyl monoacetates **29**, **30**, and **32** were mutually correlated through their transformation (Schemes VI and VII) into the same alcohol (*R*)-**91**. Unfortunately, polarimetric measurements were not useful in this case, since **91** was found to have $[\alpha]_D = 0°$. However, correlation of the three alcohols **91** obtained from **29**, **30**, and **32** was possible, by ^1H NMR analysis, after transformation into the two diastereomeric Mosher's esters by reaction with (*R*)- or (*S*)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chlorides (MTPA-Cl).[40] The remaining monoacetate **31** was correlated to **30** in a different way, which will be submitted soon.[33]

Finally, the absolute configuration of all these compounds was established through conversion of alcohol (*R*)-**97** into compound (*R*)-**100**, which was found to have the same $[\alpha]_D$ of an authentic sample prepared from commercially available (*S*)-**101** (Scheme VIII).

Conclusions

In conclusion, we have demonstrated that PPL-catalyzed monohydrolysis of 2(*E*)-alkenyl-1,3-diacetoxypropanes constitutes a very efficient entry into a series of asymmetrized tris(hydroxymethyl)methane and bis(hydroxymethyl)acetaldehyde (THYM* and BHYMA*) synthons in both enantiomeric forms. Exploitation of these new versatile chiral building blocks[42] and of their unsaturated synthetic equivalents in the stereocontrolled formation of

(33) Parallel research involving additions to the C=C double bond of **30** and of other asymmetrized (*E*)- or (*Z*)-2-alkenyl-1,3-propanediol derivatives are in progress in our laboratory, and preliminary results have already been published: Guanti, G.; Banfi, L.; Narisano, E.; Thea, S. *Tetrahedron Lett.* **1991**, *32*, 6943.

(34) **Important Notice.** During our first preparations of aldehydes (*R*)-**86–90** we experienced erratic yields in the alkoxymethyl ether formation and in the ozonolysis step, expecially when $SiR^1_2R^2$ was = $SiMe_2tBu$. In a few cases complete decomposition occurred during chromatography of **81**, **82** or during their ozonolysis. We later found that these problems were caused by the presence of impurities (mainly benzyl chlorides) in the reagents and, due to difficult chromatographic separation, in **81** and **82**. In order to obtain reproducible high yields we recommend the following: (a) do not use the commercial preparations of $BnOCH_2Cl$, which, in our hands, turned out to be very difficult to purify; on the contrary, when we prepared this reagent (according to: Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Synthesis*; Wiley: New York, 1988; Collect. Vol. VI, p 101), a single distillation gave a very pure compound, which turned out to be stable for months in a freezer if kept on anhydrous calcium chloride; (b) in the case of $PMBOCH_2Cl$, use it as freshly prepared according to ref 35b. Although the reagent is stable for few days in a freezer, appreciable decomposition takes place after 1 month; (c) quench the reaction with Et_2NH to remove most unreacted $ROCH_2Cl$; (d) never allow the crude product from these protection reactions to stay in absence of a mild base (i.e., Et_3N) which can neutralize any HCl formed by decomposition of $ROCH_2Cl$, and add 1% Et_3N to the chromatography eluent; (e) be sure to separate alkenes **81–85** from RCH_2Cl, if present; and (f) add a small quantity of pyridine (0.05–0.1 equiv) to the ozonolysis mixture after addition of Me_2S (the use of Et_3N instead of pyridine caused 10–15% racemization of the aldehyde).

(35) (a) Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1987**, *28*, 5125. (b) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.

(36) We use the term "enantiodivergent chiral building block" as a concise way to indicate a building block which can be elaborated in an enantiodivergent manner. For a definition of "enantiodivergent" see ref 1c.

(37) We have recently developed a diastereoselective allylation of aldehydes **86–90**: Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 6939.

(38) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130 and references cited therein.

(39) Mosher's ester analysis[40] of **78** and **79** showed ee ≥95% (only one diastereoisomer was detected by ^1H NMR). Treatment of **78** or **79** for 2 d at rt with $EtN(iPr)_2$ furnished the recovered alcohols with no loss of optical activity. (*R*)- and (*S*)-**84** were converted back into (*R*)- and (*S*)-**77** by reaction with n-Bu_4NF, and Mosher's ester analysis, as well as $[\alpha]_D$ measurements, indicated once again that no racemization had occurred. Finally, ^1H NMR of Mosher's esters derived from (*R*)- and (*S*)-**91**, obtained from **30** as described in Scheme VI, showed that they had not racemized.

(40) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. All Mosher's ester analyses were carried out synthesizing the two diastereoisomeric compounds using (*R*)- and (*S*)-MTPA-Cl.

(41) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(42) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320.

(43) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

C–C bonds and in C=C bond functionalization, as well as in the asymmetric synthesis of natural products, is in progress in our laboratories, and some preliminary results have been already published.[1c,3]

Moreover, a thorough study on the effect of unsaturation near the prochiral center in these hydrolyses confirmed the importance of a π system, but also uncovered an unprecedented dramatic influence of double-bond configuration. These results have been explained by proposing a new empirical model based both on polarity and steric arguments. The study has also permitted the assessment of the optimum strategy for the chemoenzymatic preparation of asymmetrized 2-alkyl-, 2-alkenyl-, and 2-alkynyl-1,3-propanediols, which represent chiral building blocks of high applicability in organic synthesis.[33]

Experimental Section

In NMR spectra, a * means that the value was obtained through double resonance experiments. Shift reagent experiments were carried out using Eu(hfc)$_3$ [tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III)]. All NMR were measured in $CDCl_3$.

All reactions employing dry solvents were carried out under a nitrogen atmosphere.

TLC analyses were carried out on silica gel plates, which were developed by spraying a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 cm^3) and H_2O (469 cm^3) and warming. R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on silica gel using the "flash" methodology.[41] Petroleum ether (40–60 °C) is abbreviated as PE.

Enzymes were purchased from Sigma (crude PPL, PLE, *Candida cylindracea lipase* (CCL), acetyl cholinesterase) or Fluka (lipase SAM-II from *Pseudomonas fluorescens*).

In extractive workup aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent at reduced pressure.

Hydrogenations were carried out under the slight pressure of H_2, given by a small inflatable balloon.

The purity of all new compounds (except for minor byproducts) was established by TLC and ^{1}H NMR, or, in some cases, also by elemental analysis and GC. Elemental analyses, GC conditions, and copies of spectra are available as supplementary material.

1,3-Diacetoxy-2-(acetoxymethyl)propane (5). A solution of 2-(hydroxymethyl)-2-nitro-1,3-propanediol (10.11 g, 66.9 mmol) in dry CH_2Cl_2 (40 mL) was treated, at room temperature, with Et_3N (65.2 mL, 468 mmol), Ac_2O (22.1 mL, 234 mmol), and DMAP (408 mg, 3.34 mmol). After being stirred overnight, the reaction was quenched with saturated aqueous NH_4Cl, stirred for 15 min, and acidified to pH 4 with HCl. Extraction with CH_2Cl_2 gave, after evaporation, a brown oil, which was taken up in hot ethanol, treated with active carbon, filtered, and evaporated again. Crystallization first with EtOH/H_2O and then with EtOH/*n*-hexane gave 1,3-diacetoxy-2-(acetoxymethyl)-2-nitropropane as a slightly yellow solid (14.14 g, 76%): mp 73–75 °C; R_f = 0.25 (*n*-hexane/Et_2O (1:1)); ^{1}H NMR (60 MHz) δ 2.12 (9 H, s, CH_3), 4.63 (6 H, s, CH_2). This product (7.38 g, 26.6 mmol) was dissolved in dry benzene (65 mL) and treated with AIBN (656 mg, 4 mmol) and Bu_3SnH (14.1 mL, 53.2 mmol). The solution was heated at reflux for 6 h. After being cooled, the solvent was removed at reduced pressure, and the residue chromatographed (*n*-hexane/Et_2O (7:3)) to give **5** as a viscous oil (5.09 g, 82%): R_f = 0.33 (*n*-hexane/Et_2O (1:1)); ^{1}H NMR (60 MHz) δ 2.11 (9 H, s, CH_3), 2.44 (1 H, heptet, CH, J = 6.4 Hz), 4.27 (6 H, d, J = 6.4 Hz, CH_2).

3-Acetoxy-2-(acetoxymethyl)-1-propanol (6). Triacetate **5** (1.912 g, 8.24 mmol) was suspended in a 0.1 M pH 7 buffer solution (KH_2PO_4–K_2HPO_4) (20 mL) and treated with crude pig pancreatic lipase (PPL) (500 mg). The pH was maintained at 7.00 by continuous addition of 1 N NaOH from an automatic burette. After consumption of 1 equiv of NaOH (8.24 mL)(≈5 h) the suspension was diluted with ether and filtered through a Celite cake. The filtrate, after separation of the phases and evaporation, gave crude **6** which was used as such for further reaction. An analytical sample of **6** (colorless oil) was obtained by chromatography (*n*-hexane/Et_2O (8:2)): R_f = 0.36 (*n*-hexane/Et_2O (1:9)), 0.40 (*n*-hexane/AcOEt (7:3)); ^{1}H NMR (80 MHz) δ 2.07 (6 H, s, CH_3C=O), 2.00–2.40 (1 H, m, CH), 2.41 (1 H, bs, OH), 3.64 (2 H, d, CH_2OH, J = 5.7 Hz), 4.17 (4 H, d, CH_2OAc, J = 6.0 Hz).

3-Acetoxy-2-(acetoxymethyl)-1-(benzyloxy)propane (8). The crude product obtained as above was dissolved in dry DMF (10 mL), cooled to 0 °C, and treated, in short sequence, with benzyl bromide (1.18 mL, 9.89 mmol) and NaH (50% suspension in mineral oil) (435 mg, 9.06 mmol). After 15 min the reaction was quenched with 15% aqueous NH_4Cl and extracted with ether to give, after evaporation and chromatography (*n*-hexane/Et_2O (1:1)), **8** as a colorless oil (1.29 g, 56% from **5**): R_f = 0.41 (*n*-hexane/Et_2O (1:1)); ^{1}H NMR (60 MHz) δ 2.12 (6 H, s, CH_3C=O), 2.20–2.80 (1 H, m, CH), 3.58 (2 H, d, CH_2OCH_2Ph, J = 6.0 Hz), 4.23 (4 H, d, CH_2OAc, J = 6.0 Hz); 4.58 (2 H, s, CH_2Ph), 7.31 (5 H, s, aromatics).

3-Acetoxy-2-(acetoxymethyl)-1-[(benzyloxy)methoxy]propane (9). Crude **6** (obtained from 4.64 mmol of **5**) was dissolved in dry CH_2Cl_2 and treated at rt with diisopropylethylamine (1.20 mL, 11.6 mmol) and benzylchloromethyl ether (see ref 34) (1 mL, 7.0 mmol). After being stirred for 2d, the reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl, evaporated to dryness, and chromatographed (*n*-hexane/CH_2Cl_2/Et_2O (4:4:1)) to give **9** as a colorless oil (1.10 g, 76%): R_f = 0.52 (*n*-hexane/AcOEt (7:3)); ^{1}H NMR (80 MHz) δ 2.04 (6 H, s, CH_3C=O), 2.32 (1 H, heptet, CH, J = 6.0 Hz), 3.62 (2 H, d, $CHCH_2O$, J = 5.8 Hz), 4.15 (4 H, d, CH_2OAc, J = 6.1 Hz), 4.58 (2 H, s, CH_2Ph), 4.74 (2 H, s, OCH_2O), 7.33 (5 H, s, aromatics).

5-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2,2-dimethyl-5-nitro-1,3-dioxane (14). A solution of **13**[9] (5.03 g, 26.3 mmol) in dry DMF (20 mL) was treated with imidazole (3.57 g, 52.44 mmol) and *tert*-butyldiphenylsilyl chloride (8.1 mL, 31.65 mmol) and stirred for 3 d at rt. The mixture was diluted with H_2O, extracted with Et_2O, and chromatographed (PE/AcOEt) to give **14** as a white solid: R_f = 0.82 (PE/AcOEt (7:3)); ^{1}H NMR (80 MHz) δ 1.02 (9 H, s, $C(CH_3)_3$), 1.34 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 4.01 (2 H, s, CH_2OSi), 4.02 and 4.39 (4 H, AB syst, CH_2OC, J = 12.6 Hz), 7.30–7.70 (10 H, m, aromatics).

3-Acetoxy-2-(acetoxymethyl)-1-[(*tert*-butyldiphenylsilyl)oxy]-2-nitropropane (16). A solution of **14** (1.90 g, 4.40 mmol) in MeOH (20 mL) was treated with *p*-toluenesulfonic acid hydrate (760 mg, 4.00 mmol) and stirred at rt for 1 h. The reaction was quenched with $NaHCO_3$ (504 mg, 6.00 mmol) and evaporated to dryness. The residue was taken up with water and extracted with AcOEt. Evaporation afforded crude diol **15**, which was acetylated in CH_2Cl_2 (25 mL) by treatment with Et_3N (4.3 cm^3, 31 mmol), Ac_2O (1.70 mL, 17.7 mmol), and DMAP (50 mg, 0.40 mmol) at rt overnight. Usual workup (see preparation of **5**) and chromatography (PE/AcOEt (9:1)) afforded **16** as a colorless oil (1.05 g, 52%); R_f = 0.50 (PE/AcOEt (7:3)); ^{1}H NMR (80 MHz) δ 1.02 (9 H, s, $C(CH_3)_3$), 2.00 (6 H, s, CH_3C=O), 4.01 (2 H, s, CH_2OSi), 4.55 (4 H, s, CH_2OAc), 7.30–7.70 (10 H, m, aromatics).

3-Acetoxy-2-(acetoxymethyl)-1-[(*tert*-butyldiphenylsilyl)oxy]propane (7). Method A. A solution of **16** (750 mg, 1.63 mmol) in dry benzene (25 mL) was treated with AIBN (135 mg, 0.80 mmol) and Bu_3SnH (0.85 mL, 3.25 mmol) and refluxed for 6 h. After cooling and evaporation of solvent, the residue was chromatographed (PE/AcOEt (9:1)) to give **7** as a colorless oil (425 mg, 63%). **Method B.** Crude **6** (obtained from 2.88 mmol of **5**) was protected by reaction with *t*BuPh$_2$SiCl (0.899 mL, 3.45 mmol) and imidazole (333 mg, 4.89 mmol) in dry DMF (4 mL) at rt for 2 d. Usual workup (see preparation of **15**) and chromatography afforded pure **7** (893 mg, 75%): R_f = 0.30 (PE/AcOEt (9:1)); ^{1}H NMR (80 MHz) δ 1.04 (9 H, s, $C(CH_3)_3$), 2.00 (6 H, s, CH_3C=O), 2.23 (1 H, heptet, CH, J = 6.0 Hz), 3.70 (2 H, d, CH_2OSi, J = 5.3 Hz), 4.17 (4 H, d, CH_2OAc, J = 6.2 Hz), 7.30–7.70 (10 H, m, aromatics).

General Procedure for Enzymatic Hydrolysis of Diacetates 7–9 with PPL, PLE, and CCL. 0.33 mmol of diacetate was suspended in a 0.1 M pH 7 buffer solution (KH_2PO_4–K_2HPO_4) and treated, at room temperature, with the enzyme (50 mg of PPL, 15 mg of CCL, 100 μL of PLE (suspension containing 11 mg/mL and 260 U/mg)). The pH was maintained constant at 7.00 by continuous addition of 0.2 N NaOH from an automatic burette. After consumption of 1 equiv (0.33 mmol) of NaOH (typical

reaction times are 4–5 h for PPL, 3 d for CCL, 3 h for PLE), the crude mixture was diluted with AcOEt and evaporated to dryness. The crude product was then purified by chromatography. Yields are reported in Table I. Ee's were measured at ^{1}H NMR in the presence of Eu(hfc)$_3$ by integration of the CH_3C=O singlets of the two enantiomers.

General Procedure for Enzymatic Hydrolysis of Diacetates 8 and 9 with Acetyl Cholinesterase. The same procedure as above was used, but the buffer was 0.02 N. Using 100 U of enzyme we had reaction times of 10 h for both substrates. **Note:** With acetyl cholinesterase the major enantiomer had the opposite configuration than that obtained with the other enzymes.

11: R_f = 0.45 (*n*-hexane/Et$_2$O (1:9)); ^{1}H NMR (80 MHz) δ 2.04 (3 H, s, CH_3C=O), 2.00–2.50 (1 H, m, CH), 3.58 (2 H, d, CH_2OBn, J = 5.6 Hz), 3.73 (2 H, d, CH_2OH, J = 5.1 Hz), 4.20 (2 H, d, CH_2OAc, J = 6.3 Hz), 4.51 (2 H, s, CH_2Ph), 7.32 (5 H, s, aromatics).

12: R_f = 0.38 (*n*-hexane/Et$_2$O (3:7)); ^{1}H NMR (80 MHz) δ 2.05 (3 H, s, CH_3C=O), 2.00–2.32 (1 H, m, CH), 3.68 (4 H, d, CH_2OCH_2OBn and CH_2OH, J = 5.7 Hz), 4.20 (2 H, d, CH_2OAc, J = 6.1 Hz), 4.60 (2 H, s, CH_2Ph), 4.75 (2 H, s, OCH_2O), 7.34 (5 H, s, aromatics).

Typical Procedure for Knoevenagel Condensation of Diethyl Malonate with Aldehydes To Give Alkylidenemalonates 17–20. A solution of isovaleraldehyde (105 mL, 1.01 mol), diethyl malonate (146.3 mL, 0.964 mol), piperidine (4.95 mL, 50 mmol), and acetic acid (14.31 mL, 0.25 mol) in dry benzene (125 mL) was refluxed in a Dean-Stark apparatus, thus removing azeotropically the water formed.[13] After 5 h no more H$_2$O formation was observed (3 h for preparation of **17**, **19**, and **20**). After being cooled the mixture was treated with brine and extracted with Et$_2$O to give a crude product which was distilled (98–103 °C (0.1 mbar)) to give a 86:14 mixture of **18** and deconjugated compound **22** (189.0 g, 89%). Compound **20** was obtained in 92% yield (bp 117–123 °C (0.035 mbar)) (it contained less than 2% of **24**). In the case of **17** and **19**, distillation (110 °C (0.03 mbar) and 100–110 °C (0.3 mbar), respectively) gave a mixture of desired product and byproducts deriving from aldehyde self-condensation. Pure products **17** and **19** (containing 15% and 25% of **21** and **23**) were obtained by chromatography (PE/Et$_2$O) (yield = 50% for **17** and 55% for **19**).

17: R_f = 0.43 (PE/Et$_2$O (9:1)); ^{1}H NMR (80 MHz) δ 0.88 (3 H, bt, CH_3CH_2C), 1.10–1.50 (8 H, m, $CH_3(CH_2)_4$–), 1.29 and 1.32 (2 × 3 H, 2t, CH_3CH_2O, J = 7.1 Hz), 2.00–2.50 (2 H, m, CH_2CH=C), 4.23 and 4.30 (2 × 2 H, 2q, CH_3CH_2O, J = 7.1 Hz), 6.99 (1 H, t, CH=C, J = 7.8 Hz). **18**: R_f = 0.57 (PE/Et$_2$O (8:2)); ^{1}H NMR (200 MHz) δ 0.94 (6 H, d, $(CH_3)_2CH$, J = 6.6 Hz), 1.29 and 1.33 (2 × 3 H, 2t, CH_3CH_2O, J = 7.1 Hz), 1.82 (1 H, nonet, $(CH_3)_2CH$, J = 6.7 Hz), 2.19 (2 H, t, CH_2CH=C, J = 7.4 Hz), 4.24 and 4.30 (2 × 2 H, 2q, CH_3CH_2O, J = 7.1 Hz), 7.01 (1 H, t, CH=C, J = 7.9 Hz). **19**: R_f = 0.47 (PE/Et$_2$O (9:1)); ^{1}H NMR (200 MHz) δ 0.91 (3 H, t, CH_3CH_2C, J = 6.9 Hz), 1.20–1.50 (4 H, m, $CH_3(CH_2)_2$), 1.29 and 1.33 (2 × 3 H, 2t, CH_3CH_2O, J = 7.1 Hz), 2.30 (2 H, q, CH_2CH=C, J = 7.5 Hz), 4.24 and 4.30 (2 × 2 H, 2q, CH_3CH_2O, J = 7.1 Hz), 7.00 (1 H, t, CH=C, J = 7.9 Hz). **20**: R_f = 0.42 (PE/Et$_2$O (9:1)); ^{1}H NMR (200 MHz) δ 1.10–1.80 (10 H, m, ring CH_2), 1.29 and 1.33 (2 × 3 H, 2t, CH_3CH_2O, J = 7.2 Hz), 2.30–2.50 (1 H, m, CHCH=C), 4.20 and 4.30 (2 × 2 H, 2q, CH_3CH_2O, J = 7.2 Hz), 6.81 (1 H, d, CH=C, J = 10.5 Hz).

(*E*)-Diethyl Hept-1-enylmalonate (21). A solution of diisopropylamine (3.20 mL, 22.6 mmol) in dry THF (30 mL) was treated, at −20 °C, with 1.6 M *n*BuLi in *n*-hexane (14.3 mL, 22.9 mmol). After 10 min HMPA (10 mL) was added and the solution, cooled to −78 °C, was treated with malonate **17** (4.82 g, 18.81 mmol), dissolved in THF (5 mL). The temperature was allowed to rise slowly (1 h 30 min) to 0 °C, and water (20 mL) was added. The pH was adjusted to ≈7 by addition of 1 N HCl, and the mixture was extracted with diethyl ether to give, after evaporation and chromatography (PE/Et$_2$O (9:1)) pure **21** as a colorless liquid (3.474 g, 72%): R_f = 0.45 (PE/Et$_2$O (9:1)); ^{1}H NMR (80 MHz) δ 0.87 (3 H, bt, CH_3CH_2C), 1.10–1.50 (6 H, m, $CH_3(CH_2)_3$–), 1.26 (6 H, t, CH_3CH_2O, J = 7.1 Hz), 1.90–2.30 (2 H, m, CH_2CH=C), 3.90–4.10 (1 H, m, CH(COOEt)$_2$), 4.20 (4 H, q, CH_3CH_2, J = 7.1 Hz), 5.60–5.80 (2 H, m, CH=CH).

Typical Procedure for Deconjugation of Malonates 18–20 with NaH in THF. To a suspension of NaH (50% in mineral oil) (50.4 g, 1.052 mol) in dry THF (450 mL), cooled to 0 °C was added a solution of **18** (160 g, 700 mmol) in dry THF (150 mL) slowly (during 45 min) (the flask should be large enough to prevent excessive frothing). The resulting suspension was stirred for 2 h at 0 °C, for 3 h at rt, and for 3 h at 40 °C. GC analysis (RSL-150 column, 130 °C for 3 min and then 3 °C/min rate; t_R = 12.78 for **22** and 14.27 for **18**) showed the reaction to be virtually complete. After further stirring overnight at rt, the suspension was slowly added to a solution of H_3BO_3 (129.8 g, 2.1 mol) in H_2O (1.2 L), kept at 0 °C. Two portions of 12 N HCl (29.2 mL, 0.35 mol) were added when half of the suspension had been added and at the end of quenching. Extraction with PE/Et$_2$O (1:1) gave after evaporation a crude oil (if some solid was present the oil was taken up with Et$_2$O and filtered),[44] which was distilled (87 °C (0.5 mbar)) to give pure **22** as a colorless liquid (112 g, 70%). GC analysis showed that **18** was less than 2%:[44] R_f = 0.57 (PE/Et$_2$O (8:2)); ^{1}H NMR (200 MHz) δ 1.00 (6 H, d, $(CH_3)_2CH$, J = 6.8 Hz), 1.27 (6 H, t, CH_3CH_2O, J = 7.1 Hz), 2.20–2.45 (1 H, m, $CH(CH_3)_2$), 3.93–3.98 (1 H, m, CH(COOEt)$_2$), 4.20 (4 H, q, OCH_2CH_3, J = 7.1 Hz), 5.55–5.75 (2 H, m, CH=CH).

By applying a similar procedure (although on a smaller scale) we prepared also **23** (14 h at rt and 3 h at 40 °C; bp = 95 °C (0.2 mbar); yield = 46%) and **24** (20 h at 50 °C; bp = 111–118 °C (0.05 mbar; yield = 50%). **23**: R_f = 0.47 (PE/Et$_2$O (9:1)); ^{1}H NMR (200 MHz) δ 0.90 (3 H, t, CH_3CH_2C, J = 7.3 Hz), 1.27 (6 H, t, CH_3CH_2O, J = 7.1 Hz), 1.42 (2 H, sextet, CCH_2CH_3, J = 7.5 Hz), 2.00–2.12 (2 H, m, CH_2CH=C), 3.93–4.00 (1 H, m, CH(COOEt)$_2$), 4.20 (4 H, q, OCH_2CH_3, J = 7.1 Hz), 5.59–5.77 (2 H, m, CH=CH). **24**: R_f = 0.38 (PE/Et$_2$O (9:1)); ^{1}H NMR (200 MHz) δ 1.27 (6 H, t, CH_3CH_2O, J = 7.1 Hz), 1.40–1.80 (6 H, m, ring CH_2), 2.10–2.20 (4 H, m, ring CH_2), 4.20 (4 H, q, OCH_2CH_3, J = 7.1 Hz), 4.28 (1 H, d, CH(COOEt)$_2$, J = 9.3 Hz), 5.42 (1 H, broad d, CH=C, J = 9.3 Hz).

(*E*)-1-Acetoxy-2-(acetoxymethyl)-3-nonene (25). A suspension of LiAlH$_4$ (11.9 g, 0.314 mol) in dry Et$_2$O (600 mL) was cooled to 0 °C and treated, during 15 min, with a solution of diester **21** (20.1 g, 78.4 mmol) in Et$_2$O (80 mL). After being stirred at 0 °C for 10 min and at rt for 3 h and 30 min, the reaction was quenched at 0 °C by careful addition of AcOEt (88 mL, 0.9 mol) followed by MeOH (10 mL) and by 3 N HCl (418 mL, 1.25 mol). The mixture was extracted with AcOEt, and the organic phase washed with brine and evaporated to dryness to give crude diol **33** (14.06 g). This diol was taken up in dry CH_2Cl_2 (160 mL), cooled to 0 °C, and treated in sequence with Et$_3$N (45.6 mL, 0.326 mol), Ac$_2$O (19.25 mL, 0.204 mol), and DMAP (498 mg, 4.08 mmol). After 30 min the ice bath was removed and the solution stirred for 20 h at rt. After quenching with saturated aqueous NH_4Cl (150 mL), the pH was adjusted to 7 by addition of 1 N HCl. Extraction with CH_2Cl_2 followed by evaporation and chromatography (PE/Et$_2$O (9:1 → 8:2)) gave pure **25** as a colorless liquid (16.6 g, 83%): R_f = 0.88 (PE/Et$_2$O (3:7)); ^{1}H NMR (200 MHz) δ 0.88 (3 H, t, CH_3CH_2C, J = 6.7 Hz), 1.10–1.50 (6 H, m, $CH_3(CH_2)_3$), 1.90–2.30 (2 H, m, CH_2CH=C), 2.05 (6 H, s, CH_3C=O), 2.69 (1 H, sextuplet, $CH(CH_2OAc)_2$, J = 6.8 Hz), 3.98–4.15 (4 H, m, CH_2OAc), 5.27 (1 H, ddt, CH=CHCH$_2$, J = 8.0, 15.4 Hz (d), 1.4 Hz (t)), 5.59 (1 H, ddt, CH=CHCH, J = 15.4, 0.8 Hz (d), 6.7 Hz (t)).

(*E*)-1-Acetoxy-2-(acetoxymethyl)-5-methyl-3-hexene (26). A suspension of LiAlH$_4$ (20.74 g, 0.546 mol) in dry Et$_2$O (500 mL) was cooled at 0 °C and treated by slow dropping with diester **22** (30 g, 0.137 mol). After being stirred for 30 min at 0 °C, and for 5 h and 30 min at rt, the reaction was cooled to 0 °C and carefully quenched by addition of a solution of NaOH (2.424 g) in H$_2$O (83 mL) (attention: the reaction is very vigorous for the first 15–20 cm^3 and so the addition must be rather slow (30–60 min)). The mixture was then stirred overnight at rt and filtered, washing the solid with Et$_2$O. The filtrate was evaporated to dryness to give crude diol **34** as a white solid (17.20 g). This solid was taken up in dry pyridine (100 mL), cooled to 0 °C, and treated with Ac$_2$O

(44) On one occasion, when the crude product contained some solid residue (most likely sodium borate) distillation led to partial (10%) isomerization to give back **18**. In the other cases (we performed this reaction on this scale five times), the **22**:**18** ratio did not change. It is advisable to keep compounds **22**–**24** in the freezer, since in one case a sample of distilled **22**, on standing for 8 months at rt, was in part isomerized to **18**.

(38.8 mL, 0.411 mol). After being stirred at 0 °C for 4 h the solvent was evaporated, the mixture taken up with Et_2O and water, the pH adjusted to 2 with 1 N HCl, and the phases separated. The organic layer was washed with $NaHCO_3$ and brine, evaporated, and distilled at 0.04 mbar (78–88 °C) to give pure **26** as a colorless liquid (21.6 g, 72%): R_f = 0.37 (PE/Et_2O (7:3)); ^1H NMR (200 MHz) δ 0.95 (6 H, d, $(CH_3)_2CH$, J = 6.8 Hz), 2.05 (6 H, s, CH_3C=O), 2.25 (1 H, octet, $CH(CH_3)_2$, J = 5.7 Hz), 2.67 (1 H, sextet, $CH(CH_2OAc)_2$, J = 6.7 Hz), 4.04 and 4.11 (4 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0 Hz, J_{AX}, J_{BX} = 6.0, 6.6 Hz), 5.22 (1 H, ddd, CH=C*H*–CH(CH_2OAc), J = 1.2, 8.0, 15.6 Hz), 5.55 (1 H, ddd, C*H*=CHCH(CH_2OAc)$_2$, J = 1.0, 6.7, 15.6 Hz).

(*E*)-1-Acetoxy-2-(acetoxymethyl)-3-heptene (27). It was prepared by the same procedure employed for **25**: yield = 40%; R_f = 0.59 (PE/Et_2O (7:3)); ^1H NMR (200 MHz) δ 0.88 (3 H, t, CH_3CH_2C, J = 7.3 Hz), 1.37 (2 H, sextet, CCH_2CH_3, J = 7.3 Hz), 1.98 (2 H, q, CH_2CH=CH, J = 7.0 Hz), 2.05 (6 H, s, CH_3C=O), 2.69 (1 H, sextet, $CH(CH_2OAc)_2$, J = 6.7 Hz), 4.05 and 4.10 (4 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0 Hz, J_{AX}, J_{BX} = 6.1, 6.6 Hz), 5.28 (1 H, ddt, CH=C*H*CH(CH_2OAc)$_2$, J = 1.3, 7.9, 15.5 Hz), 5.59 (1 H, ddt, PrC*H*=CH, J = 0.8, 15.5 (d), 6.8 (t) Hz).

1-Acetoxy-2-(acetoxymethyl)-3-cyclohexylidenepropane (28). It was prepared in 59% yield by the same procedure employed for **25**: R_f = 0.35 (PE/Et_2O (8:2)); ^1H NMR (200 MHz) δ 1.05–1.30 (6 H, m, ring CH_2), 2.00–2.20 (4 H, m, ring CH_2), 2.06 (6 H, s, CH_3C=O), 3.01 (1 H, doublet of quintuplet, $CH(CH_2OAc)_2$, J = 6.3 (quint), 9.2 Hz, (d)), 4.01 and 4.03 (4 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 10.5 Hz; J_{AX}, J_{BX} = 6.0, 6.5 Hz), 4.90 (1 H, d, C*H*=C, J = 9.2 Hz).

Typical Procedure for Hydrogenation of 25, 26, and 28 To Give 37, 38, and 39. A solution of **25** (1.00 g, 3.90 mmol) in EtOH (25 mL) was hydrogenated over 10% Pd–C (130 mg) at rt. The reaction was followed by GC (RSL-150 capillary column; 4 min at 170 °C, then 4 °C/min; t_R = 10.50 for **25** and 10.98 for **37**). When the reaction was complete, filtration, evaporation, and chromatography gave pure **37** as a colorless liquid (0.92 g, 91%): ^1H NMR (200 MHz) δ 0.88 (3 H, bt, $CH_3(CH_2)_6$), 1.15–1.55 (12 H, m, $(CH_2)_6$), 2.06 (6 H, s, CH_3C=O), 1.95–2.20 (1 H, m, C*H*), 4.03, 4.08 (4 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.1 Hz, J_{AX}, J_{BX} 5.0, 6.5 Hz).

By the same procedure we obtained **38** (80% yield) and **39** (87% yield) (saturated compounds always have higher t_R at GC). **38**: ^1H NMR (80 MHz) δ 0.87 (6 H, d, $(CH_3)_2CH$, J = 5.8 Hz), 1.20–1.70 (5 H, m, $(CH_3)_2CHCH_2CH_2$), 1.80–2.30 (1 H, m, C*H*-$(CH_2OAc)_2$), 2.05 (6 H, s, CH_3C=O), 4.05 (4 H, d, CH_2OAc, J = 5.5 Hz). **39**: ^1H NMR (80 MHz) δ 0.80–2.10 (14 H, m, ring CH_2 and C*H*, $CH_2CH(CH_2OAc)_2$), 4.07 (4 H, d, CH_2OAc, J = 5.7 Hz).

1-Acetoxy-2-(acetoxymethyl)non-3-yn-2-ol (43). A solution of *n*-heptyne (8.29 mL, 63.2 mmol) in dry THF (75 mL) was cooled to 0 °C and treated with 1.6 N *n*BuLi in hexane (37.7 mL, 60.3 mmol). The resulting solution was cooled to −78 °C and slowly treated with a solution of diacetoxyacetone[22] (10 g, 57.4 mmol) in dry THF (35 mL). After being stirred for 30 min at this temperature, the reaction was quenched with acetic acid (3.48 mL, 60.3 mmol), allowed to reach rt, and diluted with brine and Et_2O. The organic phase gave, after evaporation and chromatography (PE/Et_2O (4:6)), pure **43** as an oil (14.08 g, 91%): R_f 0.40 (PE/Et_2O (4:6)); ^1H NMR (200 MHz) δ 0.90 (3 H, bt, $CH_3(CH_2)_4$), 1.20–1.60 (6 H, m, $CH_3(CH_2)_3$), 2.13 (6 H, s, CH_3C=O), 2.20 (2 H, t, $CH_2C{\equiv}C$, J = 6.9 Hz), 2.71 (1 H, bs, O*H*), 4.19 and 4.24 (4 H, AB syst, CH_2OAc, J = 11.4 Hz).

1-Acetoxy-2-(acetoxymethyl)-5-methylhex-3-yn-2-ol (44). It was prepared in 80% yield, starting from 3-methyl-1-butyne,[45] by the same procedure described for **43**: R_f = 0.38 (PE/Et_2O (6:4)); ^1H NMR (200 MHz) δ 1.15 (6 H, d, $(CH_3)_2CH$, J = 6.9 Hz), 2.13 (6 H, s, CH_3C=O), 2.57 (1 H, heptet, $(CH_3)_2CH$, J = 6.9 Hz), 2.67 (1 H, bs, O*H*), 4.19 and 4.24 (4 H, AB syst, J = 11.3 Hz).

1-Acetoxy-2-(acetoxymethyl)hept-3-yn-2-ol (45). It was prepared in 65% yield, starting from *n*-pentyne, by the same procedure described for **43**: R_f = 0.31 (PE/Et_2O (1:1)) or 0.54 (PE/CH_2Cl_2/Et_2O (1:1:1)); ^1H NMR (200 MHz) δ 0.98 (3 H, t, $CH_3(CH_2)_2$, J = 7.3 Hz), 1.52 (2 H, sextet, CH_3CH_2, J = 7.0 Hz), 2.13 (6 H, s, CH_3C=O), 2.19 (2 H, t, $CH_2C{\equiv}C$, J = 7.1 Hz), 2.72 (1 H, bs, O*H*), 4.20 and 4.23 (4 H, AB syst, CH_2OAc, J = 11.2 Hz).

1-Acetoxy-2-(acetoxymethyl)-3-nonyne (49) and 1-Acetoxy-2-(acetoxymethyl)-2,3-nonadiene (46). A solution of alcohol **43** (6.02 g, 22.4 mmol) in dry CH_2Cl_2 (25 mL) was cooled to −40 °C and treated with Et_3N (9.43 mL, 67.2 mmol) and with methanesulfonyl chloride (3.47 mL, 44.8 mmol). The temperature was allowed to rise to −30 °C and the resulting suspension stirred for 1 h at this temperature and then quenched with H_2O (20 mL). After 15 min the mixture was warmed to rt and diluted with brine and Et_2O. The organic phase gave after evaporation a crude product (8.42 g) which was taken up in dry Et_2O (10 mL) and added to a suspension of $LiAlH_4$ (1.70 g, 44.8 mmol) in dry Et_2O (25 mL) kept at −15 °C. After being stirred for 2 h at the same temperature, the reaction was quenched cautiously with 10 N HCl (22 mL), diluted with brine, extracted with AcOEt, and evaporated to dryness. The residue was taken up in dry CH_2Cl_2 (50 mL) and treated, at 0 °C, with Et_3N (15.7 mL, 112 mmol), Ac_2O (5.28 mL, 56 mmol), and DMAP (274 mg, 2.24 mmol). After being stirred at rt for 2 h, the mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The organic layer was evaporated and chromatographed to give pure **49** (2.05 g, 36%) and **46** (280 mg, 5%) as colorless liquids. **49**: R_f = 0.33 (PE/Et_2O (7:3)); ^1H NMR (200 MHz) δ 0.90 (3 H, bt, CH_3CH_2), 1.20–1.60 (6 H, m, $CH_3(CH_2)_3$), 2.08 (6 H, s, CH_3C=O), 2.15 (2 H, dt, $CH_2C{\equiv}C$, J = 2.1 (d), 6.9 Hz (t)), 3.00 (1 H, t of quint, $CH(CH_2OAc)_2$, J = 2.2 (t), 6.2 Hz, (quint)), 4.15 (4 H, d, CH_2OAc, J = 6.2 Hz). **46**: R_f = 0.38 (PE/Et_2O (7:3)); ^1H NMR (200 MHz) δ 0.89 (3 H, bt, CH_3CH_2), 1.20–1.60 (6 H, m, $CH_3(CH_2)_3$), 2.03 (2 H, q, CH_2CH=C=C, J = 7.0 Hz), 2.07 (6 H, s, CH_3C=O), 4.60 (4 H, d, CH_2OAc, J = 2.0 Hz), 5.37 (1 H, t of quint, C*H*=C=C, J = 2.0 (quint), 7.0 Hz (t)).

1-Acetoxy-2-(acetoxymethyl)-5-methyl-3-hexyne (50) and 1-Acetoxy-2-(acetoxymethyl)-5-methyl-2,3-hexadiene (47). They were prepared in 38% and 4% yield, respectively, starting from **44** by the same procedure employed for **49** and **46**. **50**: R_f = 0.27 (PE/Et_2O (8:2)); ^1H NMR (200 MHz) δ 1.13 (6 H, d, $(CH_3)_2CH$, J = 6.8 Hz), 2.08 (6 H, s, CH_3C=O), 2.52 (1 H, d of heptet, $(CH_3)_2CH$, J = 2.1 (d), 6.8 Hz (hept)), 2.99 (1 H, d of quint, $CH(CH_2OAc)_2$, J = 2.0 (d), 6.2 Hz (quint)), 4.15 (4 H, d, CH_2OAc, J = 6.2 Hz). **47**: R_f = 0.37 (PE/Et_2O (8:2)); ^1H NMR (200 MHz) δ 1.01 (6 H, d, $(CH_3)_2CH$, J = 6.8 Hz), 2.07 (6 H, s, CH_3C=O), 2.28–2.40 (1 H, m, $(CH_3)_2CH$), 4.61 (4 H, d, CH_2OAc, J = 2.1 Hz), 5.40 (1 H, d of quint, C*H*=C=C, J = 2.1 (quint), 5.9 Hz (d)).

1-Acetoxy-2-(acetoxymethyl)-3-heptyne (51). It was prepared in 40% yield starting from **45**, by the same procedure employed for **49**. In this case we did not obtain appreciable amounts of allene **48**: R_f = 0.32 (PE/Et_2O (8:2)); ^1H NMR (200 MHz) δ 0.96 (3 H, t, CH_3CH_2, J = 7.3 Hz), 1.50 (2 H, sextet, CH_3CH_2, J = 7.2 Hz), 2.08 (6 H, s, CH_3C=O), 2.14 (2 H, dt, $CH_3CH_2CH_2$, J = 2.1 (d), 7.0 Hz (t)), 3.01 (1 H, t of quint, C*H*-$(CH_2OAc)_2$, J = 2.1 (t), 6.2 Hz (quint)), 4.15 (4 H, d, CH_2OAc, J = 6.2 Hz).

(*Z*)-1-Acetoxy-2-(acetoxymethyl)-3-nonene (52). A solution of alkyne **49** (1.0 g, 3.92 mmol) and 2,6-lutidine (0.25 mL) in EtOH (30 mL) was hydrogenated over Lindlar catalyst (100 mg) for 5 h at rt. The reaction was followed by GC (Superox capillary column; 3 min at 170 °C and then 3 °C/min; t_R = 9.60 for **52**, 11.54 for **49**, and 12.60 for **37**). After filtration of the catalyst, evaporation, and chromatography (PE/Et_2O (7:3)), pure **52** as a colorless liquid was obtained (958 mg, 95%): R_f = 0.33 (PE/Et_2O (7:3)); ^1H NMR (200 MHz) δ 0.89 (3 H, bt, CH_3CH_2), 1.20–1.50 (6 H, m, $CH_3(CH_2)_3$), 2.06 (6 H, s, CH_3C=O), 2.00–2.20 (2 H, m, CH_2CH=CH), 3.07 (1 H, d of quint, $CH(CH_2OAc)_2$, J = 6.2 (quint), 10.2 Hz (d)), 4.05 (4 H, d, CH_2OAc, J = 6.2 Hz), 5.20 (1 H, tt, C*H*=CHCH$_2$, J = 1.5, 10.2 Hz), 5.60 (1 H, ddt, C*H*=CHCH, J = 7.4 (t), 10.5 (d), 1.0 Hz (d)).

(*Z*)-1-Acetoxy-2-(acetoxymethyl)-5-methyl-3-hexene (53). It was prepared in 80% yield starting from **50** by the same procedure used for **52** (the reaction was slightly slower): GC: Superox capillary column; 3 °C/min starting from 130 °C; t_R = 10.84 for **53** and 12.86 for **50**; R_f = 0.27 (PE/Et_2O (8:2)); ^1H NMR (200 MHz) δ 0.97 (6 H, d, $(CH_3)_2CH$, J = 6.6 Hz), 2.06 (6 H, s, CH_3C=O), 2.60 (1 H, d of heptet, $CH(CH_3)_2$, J = 10.2 (d), 6.6 Hz (hept)), 3.09 (1 H, d of quint, $CH(CH_2OAc)_2$, J = 9.5 (d), 6.4 Hz (quint)), 4.04 (4 H, d, CH_2OAc, J = 6.4 Hz), 5.07 (1 H, t,

(45) Miller, H. N.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Org. Chem.* **1954**, *19*, 1883.

CH=CHCH(CH_3)$_2$, J = 10.6 Hz), 5.42 (1 H, t, CH=CHCH(CH_2OAc)$_2$, J = 10.6 Hz).

(*Z*)-1-Acetoxy-2-(acetoxymethyl)-3-heptene (54). It was prepared in 80% yield starting from **51** by the same procedure used for **52** except that 2,6-lutidine was omitted: GC: Superox capillary column; 3 °C/min starting from 130 °C; t_R = 11.69 for **54** and 13.46 for **51**); R_f = 0.32 (PE/Et_2O (8:2)); ^{1}H NMR (200 MHz) δ 0.92 (3 H, t, CH_3CH_2, J = 7.3 Hz), 1.40 (2 H, sextet, CH_2CH_3, J = 7.3 Hz), 2.06 (6 H, s, CH_3C=O), 1.97–2.15 (2 H, m, CH_2CH=CH), 3.08 (1 H, dd of quint, CH(CH_2OAc)$_2$, J = 6.3 (quint), 1.0 (d), 9.5 Hz (d)), 4.05 (4 H, d, CH_2OAc, J = 6.3 Hz), 5.22 (1 H, tt, CH=CHCH_2, J = 1.5, 10.3 Hz), 5.59 (1 H, ddt, CH=CHCH, J = 1.0, 10.6 (d), 7.7 Hz (t)).

General Procedure for Enzymatic Hydrolyses of Diacetates 25–28, 37–39, and 49–54 (Tables II and III). (a) Analytical Scale. A suspension of crude PPL (Sigma, cat. L 3126) (110 mg) in 7 mL of pH 7 0.02 M buffer solution (K_2HPO_4–KH_2PO_4) (or 7 mL of a mixture of buffer solution and organic cosolvent), kept at 25 °C, was adjusted precisely to pH 7.00 by addition of 1 M NaOH from an automatic burette. Then the required diacetate (1.00 mmol) was added through syringe and the pH maintained constant through automatic addition of 1 M NaOH. The rate of consumption of NaOH allowed the determination of the initial and final rate. After addition of 1.00 mmol of base (1–5 h), the suspension was diluted with Et_2O (15 mL) and brine (10 mL), saturated by addition of solid NaCl, and filtered through a Celite cake. The resulting mixture was extracted with Et_2O and evaporated. A sample of the crude product was used for checking the conversion (which resulted always in the range 47–53%), and of the relative percent of diacetate, monoacetate, and diol. Conversion (C), defined as = [[$^1/_2$(mol of monoacetate) + (mol of diol)]/[(mol of diacetate) + (mol of monoacetate) + (mol of diol)]]100 was given by [(integral of CH_2OH signals)/[(integral of CH_2OH signals) + (integral of CH_2OAc signals)]]100. Usually it was possible also to measure the ratio of integral of CH_2OH (diol)/integral of CH_2OH (monoacetate) (called Z) or the ratio CH_2OAc (diacetate)/CH_2OAc (monoacetate) (Y) or the ratio CH_3C=O (diacetate)/CH_3C=O (monoacetate) (Y). Then % monoacetate was $C/[(Z + 1)/2]$ = $(100 - C)/[(Y + 1)/2]$. Only in the case of hydrolysis of diacetate **25** (because the spectra were taken at 80 MHz) it was not possible to determine the % monoacetate in this way. The data reported in Table II were in this case obtained by weight of isolated products.

The crude products were chromatographed (PE/Et_2O) to give pure monoacetates **29–32** and **55–63**. $[\alpha]_D$ were measured at c 2 in $CHCl_3$. Ee's were determined by ^{1}H NMR in the presence of Eu(hfc)$_3$ by integration of the CH_3C=O signals. In all cases this method was previously standardized by examination of racemic monoacetate, obtained by treating a solution of diacetate (1 mmol) in THF (5 mL) and MeOH (0.5 mL) with 1 N aqueous NaOH (0.27 mL) for 5 min at rt.

(b) Preparative Scale. As above, but we used 3 mL of solvent and 80 mg of PPL for each mmol of substrate, and the buffer was 0.1 N.

^{1}H NMR Characterization of Monoacetates 29, 31, 32, and 55–63. 29: (200 MHz) δ 0.86 (3 H, bt, CH_3CH_2, J = 6.6 Hz), 1.15–1.45 (6 H, m, $CH_3(CH_2)_3$), 1.80 (1 H, t, OH, J = 6.4 Hz), 1.99 (2 H, q, CH_2CH=CH, J = 6.8 Hz), 2.04 (3 H, s, CH_3C=O), 2.51 (1 H, sextet, CHCH=CHCH_2, J = 7.0 Hz), 3.42–3.65 (2 H, m, CH_2OH), 4.05 and 4.16 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0, J_{AX}, J_{BX} = 5.5, 7.1 Hz), 5.26 (1 H, dd, CH=CHCH_2, J = 8.2, 15.6 Hz), 5.60 (1 H, dt, CH=CHCH, J = 8.8, 15.6 Hz). **31**: (200 MHz) δ 0.89 (3 H, t, CH_3CH_2, J = 7.3 Hz), 1.39 (2 H, sextet, CH_2CH_3, J = 7.3 Hz), 1.78 (1 H, t, OH, J = 6.3 Hz), 1.96–2.09 (2 H, m, CH_2CH=CH), 2.07 (3 H, s, CH_3C=O), 2.54 (1 H, sextet, CHCH=CH, J = 6.6 Hz), 3.52–3.64 (2 H, m, CH_2OH), 4.08 and 4.18 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0, J_{AX}, J_{BX} = 5.5, 7.0 Hz), 5.29 (1 H, ddt, CH=CHCH, J = 1.4 (t), 8.1, 15.5 Hz (d)); 5.55–5.70 (1 H, m, CH_2CH=CH). **32**: (200 MHz) δ 1.55 (6 H, bs, ring CH_2), 1.84 (1 H, dd, OH, J = 5.8, 7.3 Hz), 2.07 (3 H, s, CH_3C=O), 2.05–2.25 (4 H, m, ring CH_2), 2.86 (1 H, d of quint, CHCH$_2$OH, J = 9.2 (d), 6.4 Hz (quint)), 3.40–3.68 (2 H, m, CH_2OH), 4.02 and 4.12 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0, J_{AX}, J_{BX} = 5.6, 7.1 Hz), 4.92 (1 H, d, CH=C, J = 9.4 Hz). **55**: (200 MHz) δ 0.87 (3 H, bt, CH_3CH_2, J = 6.4 Hz), 1.15–1.50 (12 H, m, $CH_3(CH_2)_3$), 1.70–1.90 (1 H, m, CHCH$_2$OH), 1.90–2.00 (1 H, m, OH), 2.07 (3 H, s, CH_3C=O), 3.40–3.70 (2 H, m, CH_2OH), 4.08 and 4.20 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.1, J_{AX}, J_{BX} = 4.3, 6.7 Hz). **56**: (200 MHz) δ 0.89 (6 H, d, (CH_3)$_2$CH, J = 6.6 Hz), 1.15–1.40 (4 H, m, $CH_3(CH_2)_2$), 1.53 (1 H, nonet, CH(CH$_3$)$_2$, J = 6.5 Hz), 1.70–1.85 (1 H, m, CHCH$_2$OH), 1.97 (1 H, t, OH, J = 5.9 Hz), 2.08 (3 H, s, CH_3C=O), 3.45–3.70 (2 H, m, CH_2OH), 4.09 and 4.21 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.2, J_{AX}, J_{BX} = 4.4, 6.7 Hz). **57**: (200 MHz) δ 0.80–1.40 (6 H, m, ring CH_2), 1.56–1.80 (4 H, m, ring CH_2), 1.85–2.05 (1 H, m, ring CH), 2.08 (3 H, s, CH_3C=O), 3.40–3.70 (2 H, m, CH_2OH), 4.05 and 4.20 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.2, J_{AX}, J_{BX} = 4.2, 6.8 Hz). **58**: (200 MHz) δ 0.90 (3 H, bt, CH_3CH_2), 1.25–1.60 (6 H, m, $CH_3(CH_2)_3$), 2.01 (1 H, t, OH, J = 6.8 Hz), 2.09 (3 H, s, CH_3C=O), 2.17 (2 H, dt, CH_2C≡C, J = 2.2 (d), 6.9 Hz (t)), 2.80–2.95 (m center = 2.88) (1 H, m, CHCH$_2$OH), 3.65 (2 H, t, CH_2OH, J = 6.1 Hz), 4.13 and 4.25 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 10.9, J_{AX}, J_{BX} = 5.4, 7.5 Hz). **59**: (200 MHz) δ 1.15 (6 H, d, (CH_3)$_2$CH, J = 6.9 Hz), 2.00 (1 H, t, OH, J = 6.8 Hz), 2.08 (3 H, s, CH_3C=O), 2.55 (1 H, d of heptet, CH(CH$_3$)$_2$, J = 2.0 (d), 6.9 Hz), 2.87 (1 H, ddq, CHCH$_2$OH, J = 2.0, 7.5 (d), 5.4 Hz (q)), 3.64 (2 H, t, CH_2OH, J = 5.5 Hz), 4.12 and 4.25 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 10.9 Hz, J_{AX}, J_{BX} = 5.2, 7.8 Hz). **60**: (200 MHz) δ 0.97 (3 H, t, CH_3CH_2, J = 7.3 Hz), 1.52 (2 H, sextet, CH_3CH_2, J = 7.2 Hz), 2.01 (1 H, t, OH, J = 6.9 Hz), 2.08 (3 H, s, CH_3C=O), 2.16 (2 H, dt, CH_2C≡C, J = 2.2 (d), 7.0 Hz (t)), 2.81–2.96 (1 H, m, CHC≡C), 3.65 (2 H, t, CH_2OH, J = 6.2 Hz), 4.13, 4.25 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 10.9 Hz, J_{AX}, J_{BX} = 5.3, 7.5 Hz). **61**: (200 MHz) δ 0.89 (3 H, bt, CH_3CH_2), 1.20–1.50 (6 H, m, $CH_3(CH_2)_3$), 1.86 (1 H, t, OH, J = 6.7 Hz), 2.00–2.20 (2 H, m, CH_2CH=CH), 2.08 (3 H, s, CH_3C=O), 2.93 (1 H, dd of quint, CHCH=CHCH_2, J = 1.0, 9.7 (d), 6.6 Hz (quint)), 3.45–3.67 (2 H, m, CH_2OH), 4.06 and 4.15 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0 Hz, J_{AX}, J_{BX} = 5.6, 6.8 Hz), 5.22 (1 H, ddt, CH=CHCH_2, J = 1.5 (t), 9.7, 10.9 Hz (d)), 5.64 (1 H, ddt, CH=CHCH, J = 7.3 (t), 1.0, 10.9 Hz (d)). **62**: (200 MHz) δ 0.98 (6 H, d, (CH_3)$_2$CH, J = 6.6 Hz), 1.82 (1 H, t, OH, J = 6.3 Hz), 2.07 (3 H, s, CH_3C=O), 2.60 (1 H, d of heptet, CH(CH$_3$)$_2$, J = 6.6 (hept), 9.9 Hz (d)), 2.93 (1 H, d of quint, CHCH$_2$OH, J = 6.2 (quint), 9.7 (d)), 3.45–3.67 (2 H, m, CH_2OH), 4.06 and 4.14 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0 Hz, J_{AX}, J_{BX} = 5.8, 6.8 Hz), 5.08 (1 H, t, CH_2CH=CH, J = 10.3 Hz), 5.47 (1 H, t, CHCH=CH, J = 10.3 Hz). **63**: (200 MHz) δ 0.92 (3 H, t, CH_3, J = 7.3 Hz), 1.40 (2 H, sextet, CH_2CH_3, J = 7.4 Hz), 1.82 (1 H, dd, OH, J = 7.0, 5.5 Hz), 2.01–2.13 (2 H, m, CH_2CH=CH), 2.07 (3 H, s, CH_3C=O), 2.84–3.01 (1 H, m, CHCH=CH), 3.45–3.70 (2 H, m, CH_2OH), 4.07 and 4.15 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.1 Hz, J_{AX}, J_{BX} = 5.6, 6.8 Hz), 5.17–5.29 (1 H, m, CH_2CH=CH, $J_{3,4}$ = 11.0 Hz*), 5.58–5.71 (1 H, m, CHCH=CH, $J_{3,4}$ = 11.0 Hz*).

^{1}H NMR Characterization of Some of the Diols 33–36 and 64–72. 33: (60 MHz) δ 0.90 (3 H, bt, CH_3CH_2), 1.05–1.75 (6 H, m, $CH_3(CH_2)_3$), 1.80–2.25 (1 H, m, CH_2CH=CH), 2.48 (1 H, sextet, CH(CH$_2$OH)$_2$, J = 6.6 Hz), 2.97 (2 H, bs, OH), 3.76 (4 H, d, CH_2OH, J = 6.4 Hz), 5.36 (1 H, dd, CH=CHCH$_2$, J = 7.0, 16.3 Hz), 5.72 (1 H, dt, CH=CHCH, J = 6.1, 16.3 Hz). **35**: (200 MHz) δ 0.89 (3 H, t, CH_3CH_2, J = 7.3 Hz), 1.39 (2 H, sextet, CH_2CH_3, J = 7.3 Hz), 1.96 (2 H, bs, OH), 2.02 (2 H, q, CH_2CH=CH, J = 7.0 Hz), 2.50 (1 H, sextet, CHCH=CH, J = 6.8 Hz), 3.71 (4 H, d, CH_2OH, J = 6.2 Hz), 5.26 (1 H, ddt, CH=CHCH, J = 1.3, (t), 8.1, 15.6 Hz (d)), 5.56–5.70 (1 H, m, CH_2CH=CH). **36**: (200 MHz) δ 0.82–1.75 (6 H, bs, ring CH_2), 1.95 (2 H, bs, OH), 2.10–2.22 (4 H, m, ring CH_2), 2.74–2.94 (1 H, m, CHCH$_2$OH), 3.60–3.67 (4 H, m, CH_2OH), 4.82 (1 H, dt, CH=C, J = 9.4 (d), 1.1 Hz (t)). **67**: (200 MHz) δ 0.90 (3 H, bt, CH_3CH_2), 1.20–1.60 (6 H, m, $CH_3(CH_2)_3$), 2.18 (2 H, dt, CH_2C≡C, J = 2.2 (d), 7.0 Hz (t)), 2.52 (2 H, bs, OH), 2.70–2.85 (1 H, m, CHC≡C), 3.75 (4 H, d, CH_2OH, J = 5.6 Hz). **69**: (200 MHz) δ 0.97 (3 H, t, CH_3CH_2, J = 7.3 Hz), 1.52 (2 H, sextet, CH_3CH_2, J = 7.2 Hz), 1.93 (2 H, t, OH, J = 6.2 Hz), 2.17 (2 H, dt, CH_2C≡C, J = 2.3 (d), 7.1 Hz (t)), 2.73–2.86 (1 H, m, CHC≡C), 3.76 (4 H, t, CH_2OH, J = 5.3 Hz). **70**: (200 MHz) δ 0.86 (3 H, bt, CH_3CH_2, J = 6.6 Hz), 1.20–1.50 (6 H, m, $CH_3(CH_2)_3$); 1.95 (2 H, bt, OH), 2.00–2.20 (2 H, m, CH_2CH=, mc = 2.10 ppm), 2.80–3.00 (1 H, m, CHC≡C, mc = 2.90 ppm), 3.60–3.80 (4 H, m, CH_2OH), 5.14 (1 H, tt, CH=CHCH$_2$, J = 1.6,

10.3 Hz), 5.64 (1 H, ddt, C*H*=CHCH, J = 1.0 (d), 10.3 (d), 7.3 Hz (t)). **72**: (200 MHz) δ 0.92 (3 H, t, CH_3, J = 7.3 Hz), 1.40 (2 H, sextet, CH_2CH_3, J = 7.3 Hz), 1.90–2.20 (2 H, m, O*H*), 2.08 (2 H, q, CH_2CH=CH, J = 7.3 Hz), 2.80–2.98 (1 H, m, *CH*CH=CH, mc = 2.89 ppm), 3.66 and 3.70 (4 H, AB part of an ABX syst, CH_2OH, J_{AB} = 10.6 Hz, J_{AX}, J_{BX} = 5.0, 8.1 Hz), 5.15 (1 H, t, CH=C*H*CH, J = 9.5 Hz, J_{vic} = 10.7 Hz*), 5.63 (1 H, dt, CH_2C-*H*=CH, J = 10.9 (d), 7.4 (t)).

(*S*)-(*E*)-2-(Acetoxymethyl)-5-methylhex-3-en-1-ol (30). A suspension of crude PPL (Sigma, cat. L 3126) (4 g) in 150 mL of pH 7 0.05 M buffer solution (K_2HPO_4–KH_2PO_4) and 26.5 mL of diisopropyl ether, kept at 25 °C, was adjusted precisely to pH 7.00 by addition of 1 M NaOH from an automatic burette. Then diacetate **26** (9.0 mL, 8.852 g, 38.77 mmol) was added through a syringe and the pH maintained constant through automatic addition of 1 M NaOH. After addition of 1.00 mmol of base (38.77 mL) (1.5–3 h), the suspension was diluted with Et_2O (150 mL) and brine (100 mL), saturated by addition of solid NaCl, and filtered through a Celite cake. The phases were separated, and the aqueous phase was reextracted twice with Et_2O. The reunited organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. Chromatography through 150 g of silica gel eluted with PE/Et_2O (1:1 → 4:6) gave pure **30** as a colorless liquid (5.45 g, 75%): R_f = 0.38 (PE/Et_2O (1:1)); $[\alpha]_D$ = −25.3° (*c* 2, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.98 (6 H, d, $(CH_3)_2CH$, J = 6.7 Hz), 1.83 (1 H, t, O*H*, J = 5.9 Hz), 2.07 (3 H, s, CH_3C=O), 2.29 (1 H, octet, $CH(CH_3)_2$, J = 6.5 Hz), 2.52 (1 H, sextet, *CH*CH_2OH, J = 6.8 Hz), 3.46–3.70 (2 H, m, CH_2OH), 4.07 and 4.19 (2 H, AB part of an ABX syst, CH_2OAc, J_{AB} = 11.0 Hz, J_{AX}, J_{BX} = 5.5, 7.1 Hz), 5.24 (1 H, ddd, C*H*=CH*i*Pr, J = 15.6, 8.2, 1.2 Hz), 5.61 (1 H, dd, C*H*=CHCH$_2$OH, J = 15.6, 6.6 Hz); ^{13}C NMR (50 MHz) δ 171.27 (*C*=O); 142.00 and 123.41 (*C*=*C*), 64.64 and 63.02 (CH_2O), 44.46 ($CHCH_2OH$), 31.22 ($CH(CH_3)_2$), 22.43 ($(CH_3)_2CH$), 20.81 (CH_3C=O); IR (liquid film): ν_{max} 3459 (broad), 2958, 2867, 1743, 1467, 1384, 1366, 1256, 1037, 976 cm^{-1}.

General Procedure for Reduction of Monoacetates 29–32 and 58–63 to the Corresponding Saturated Monoacetates. A solution of unsaturated monoacetate (1.0 mmol) in EtOH (15 mL) was hydrogenated over 10% Pd on carbon (30 mg). The reaction was followed at GC (capillary SUPEROX column). After filtration of the catalyst, the solvent was evaporated and the product purified through chromatography. Yields were usually >80%.

(*R*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-5-methylhex-3-en-1-ol (76). A solution of monoacetate **30** (3.78 g, 20.31 mmol) in dry CH_2Cl_2 (60 cm^3) was treated at rt with diisopropylethylamine (5.301 mL, 30.44 mmol) and freshly distilled benzyl chloromethyl ether (see note 34) (4.24 mL, 30.44 mmol). After 3 h and 30 min the reaction was complete and the mixture was diluted with saturated aqueous NH_4Cl, extracted with Et_2O, and evaporated to give a crude product (6.87 g). It was taken up in MeOH (90 mL) and treated with Et_3N (1.70 mL, 12.19 mmol) (to quench excess of BOM-Cl). After stirring for 2 h and 30 min at rt, the solution was treated with 1 N KOH in MeOH (50.8 mL, 50.8 mmol) and stirred until reaction was complete by TLC (2 h). The solution was added to 100 mL of 0.45 M pH 4 buffer solution [$(NH_4)H_2PO_4$] cooled at 0 °C. After evaporation of most MeOH, the mixture was extracted with Et_2O to give, after evaporation and chromatography (PE/Et_2O), pure **76** as a colorless oil (4.89 g, 91%): R_f = 0.32 (PE/Et_2O (67:33)); $[\alpha]_D$ = +19.5° (*c* 2, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.98 (6 H, d, $(CH_3)_2CH$, J = 6.7 Hz), 2.09 (1 H, t, O*H*, J = 6.0 Hz), 2.28 (1 H, d of octet, $CH(CH_3)_2$, J = 1.2 (d), 6.6 Hz), 2.54 (1 H, sextet, *CH*CH_2OH, J = 7.1 Hz), 3.54–3.78 (4 H, m, CH_2OH, CH_2OBOM), 4.61 (2 H, s, CH_2Ph), 4.76 (2 H, s, OCH_2O), 5.25 (1 H, ddd, C*H*=CH*i*Pr, J = 15.6, 8.0, 1.2 Hz), 5.61 (1 H, dd, C*H*=CHCH$_2$OH, J = 15.6, 6.5 Hz), 7.25–7.40 (5 H, m, aromatics).

(*R*)-(*E*)-2-[[[(*p*-Methoxybenzyl)oxy]methoxy]methyl]-5-methylhex-3-en-1-ol (77). It was prepared in 79% yield by the same procedure employed for **76**: R_f 0.27 (PE/Et_2O (1:1)); $[\alpha]_D$ = +22.4° (*c* 2, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.98 (6 H, d, $(CH_3)_2CH$, J = 6.8 Hz), 1.58 (1 H, bs, O*H*), 2.28 (1 H, d of octet, $CH(CH_3)_2$, J = 1.2 (d), 6.7 Hz), 2.54 (1 H, d of sextet, *CH*CH_2OH, J = 0.7 (d), 6.7 Hz), 3.55–3.77 (4 H, m, CH_2O), 3.81 (3 H, s, OCH_3), 4.54 (2 H, s, CH_2Ar), 4.73 (2 H, s, OCH_2O), 5.25 (1 H, ddd, C*H*=CH*i*Pr, J = 1.2, 8.0, 15.7 Hz), 5.59 (1 H, ddd, C*H*=CHC-HCH_2OH, J = 0.7, 6.5, 15.7 Hz), 6.84–6.94 (2 H, m, aromatics), 7.24–7.33 (2 H, m, aromatics).

(*R*)-(*E*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5-methylhex-3-en-1-ol (78). A solution of monoacetate **30** (5.45 g, 29.26 mmol) in dry DMF (20 mL), was cooled to 0 °C and treated with Me_2tBuSiCl (5.29 g, 35.09 mmol) and imidazole (4.84 g, 71.09 mmol). After 10 min the reaction was allowed to reach rt and stirred for 2 h and 30 min. After being cooled to 0 °C, the solution was treated with H_2O (100 mL), extracted with PE/Et_2O (1:1), and evaporated to dryness. This crude product was taken up in MeOH (20 mL), cooled to 0 °C, and treated with a solution of KOH (2.46 g, 43.9 mmol) in MeOH (200 mL). The solution was stirred for 2 h at 0 °C, and for 1 h at rt, and treated with saturated aqueous NH_4Cl (20 mL). Most methanol was evaporated at reduced pressure and the mixture diluted with H_2O and extracted with Et_2O to give, after evaporation and chromatography, pure **78** as a colorless oil (6.63 g, 88%): R_f = 0.40 (PE/Et_2O (8:2)); $[\alpha]_D$ = +23.0° (*c* 2 $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.07 (6 H, s, CH_3Si), 0.90 (9 H, s, $(CH_3)_3C$), 0.97 (6 H, d, $(CH_3)_2CH$, J = 6.8 Hz), 2.25 (1 H, d of octet, $CH(CH_3)_2$, J = 1.2 (d), 6.7 Hz), 2.35–2.55 (1 H, m, *CH*CH_2OH), 2.59 (1 H, t, O*H*, J = 5.8 Hz), 3.55–3.80 (4 H, m, CH_2O), 5.19 (1 H, ddd, C*H*=CH*i*Pr, J = 15.6, 8.0, 1.2 Hz), 5.55 (1 H, ddd, C*H*=CHCH$_2$OH, J = 1.0, 15.6, 6.5 Hz).

(*R*)-(*E*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-methylhex-3-en-1-ol (79). It was prepared from **30** and Ph_2tBuSiCl in 83% yield following the same procedure used for **78**: R_f = 0.22 (PE/Et_2O (8:2)); $[\alpha]_D$ = +14.3° (*c* 2.5 $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.94 (6 H, d, $(CH_3)_2CH$, J = 6.7 Hz), 1.05 (9 H, s, $(CH_3)_3C$), 2.10–2.35 (1 H, m, $CH(CH_3)_2$, mc 2.23 ppm), 2.26 (1 H, t, O*H*, J = 6.0 Hz), 2.40–2.58 (1 H, m, *CH*CH_2OH, mc 2.48 ppm), 3.58–3.85 (4 H, m, CH_2O), 5.19 (1 H, ddd, C*H*=CH*i*Pr, J = 15.6, 8.1, 1.2 Hz), 5.51 (1 H, ddd, C*H*=CHCH$_2$OH, J = 0.7, 15.6, 6.6 Hz), 7.30–7.50 (6 H, m, aromatics), 7.60–7.75 (4 H, m, aromatics).

(*R*)-(*E*)-5-Methyl-2-[[(triisopropylsilyl)oxy]methyl]hex-3-en-1-ol (80). A solution of **30** (809 mg, 4.34 mmol) in dry CH_2Cl_2 (20 mL) was treated at 0 °C with 2,6-lutidine (0.81 mL, 8.68 mmol) and triisopropylsilyl triflate (1.725 mL, 6.51 mmol). After being stirred for 4 h at 0 °C, the mixture was treated with brine, extracted with Et_2O, evaporated, and chromatographed to give pure 1-acetoxy-5-methyl-2-[[(triisopropylsilyl)oxy]methyl]hex-3-ene as a colorless oil (1.26 g, 85%): R_f = 0.66 (PE/Et_2O (95:5)); $[\alpha]_D$ = +7.3° (*c* 2.2 $CHCl_3$). This compound was taken up in MeOH (27 mL) and treated at 0 °C with KOH (308 mg, 5.5 mmol). After 2 h the temperature was raised to rt and the solution stirred overnight. Usual workup (see preparation of **78**) and chromatography afforded pure **80** as a colorless oil (1.083 g, 98%, 83% from **30**): R_f = 0.37 (PE/Et_2O (8:2)); $[\alpha]_D$ = +19.8° (*c* 2.26, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.97 (6 H, d, $(CH_3)_2CHC$, J = 6.8 Hz), 1.00–1.20 (21 H, m, $(CH_3)_2CHSi$), 2.25 (1 H, d of octet, $CCH(CH_3)_2$, J = 1.2 (d), 6.7 Hz), 2.38–2.58 (1 H, m, *CH*CH_2OH), 3.67 and 3.85 (2 H, AB part of an ABX syst, CH_2O, J_{AB} = 9.7 Hz, J_{AX}, J_{BX} = 4.6, 5.0 Hz), 3.74 and 3.75 (2 H, AB part of an ABX syst, CH_2O, J_{AB} = 10.1 Hz, J_{AX}, J_{BX} = 10.3, 4.8 Hz), 5.20 (1 H, ddd, C*H*=CH*i*Pr, J = 1.2, 8.1, 15.6 Hz), 5.54 (1 H, ddd, C*H*=CHCH$_2$OH, J = 0.8, 6.4, 15.6 Hz).

(*R*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-1-[(*tert*-butyldimethylsilyl)oxy]-5-methylhex-3-ene (81). A solution of **78** (1.57 g, 6.07 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 °C and treated with $EtN(iPr)_2$ (1.768 mL, 10.33 mmol) and with freshly distilled benzyl chloromethyl ether (see note 34) (1.266 mL, 9.105 mmol). After the solution was stirred for 30 min at 0 °C and 6 h at rt, diethylamine (0.441 mL, 4.249 mmol) was added and the solution stirred for 15 min, diluted with brine, and extracted with Et_2O. The organic phase, after evaporation, was immediately chromatographed (PE/Et_2O containing 1% of Et_3N) to give pure (*R*)-**81** as a colorless oil (2.110 g, 92%): R_f = 0.44 (PE/Et_2O (95:5)); $[\alpha]_D$ = +1.9° (*c* 2, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.04 (6 H, s, $(CH_3)_2Si$), 0.89 (9 H, s, $(CH_3)_3C$), 0.97 (6 H, d, $(CH_3)_2CH$, J = 6.7 Hz), 2.26 (1 H, octet, $CH(CH_3)_2$, J = 6.6 Hz), 2.42 (1 H, d of quint, *CH*CH_2O, J = 6.1 (quint), 7.8 Hz (d)), 3.61 (2 H, d, CH_2O, J = 6.1 Hz), 3.59 and 3.66 (2 H, AB part of an ABX syst, CH_2O, J_{AB} = 9.5 Hz, J_{AX}, J_{BX} = 6.0, 6.1 Hz), 4.60 (2 H, s, CH_2Ph), 4.75 (2 H, s, OCH_2O), 5.32 (1 H, ddd, C*H*=CH*i*Pr, J = 1.0, 7.8, 15.6 Hz), 5.53 (1 H, dd, C*H*=CHCH$_2$O, J = 6.1,

15.6 Hz), 7.25–7.40 (5 H, m, aromatics).

(*S*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-1-[(*tert*-butyldimethylsilyl)oxy]-5-methylhex-3-ene (81). A solution of **76** (974 mg, 3.68 mmol) in dry DMF (10 mL) was treated at 0 °C with imidazole (760 mg, 11.05 mmol) and $Me_2tBuSiCl$ (833 mg, 5.53 mmol). After 15 min at 0 °C and 2 h at rt, the reaction was quenched with H_2O, extracted with PE/Et_2O (1:1), evaporated, and chromatographed to give pure (*S*)-**81** as a colorless oil (1.210 g, 87%): $[\alpha]_D$ = −1.7° (*c* 2, $CHCl_3$).

(*R*)-(*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-5-methylhex-3-ene (82). It was prepared from **78** and freshly prepared $PMBOCH_2Cl$ (see note 34) in 85% yield by the same procedure employed for (*R*)-**81**: R_f = 0.33 (PE/Et_2O (95:5)); ^1H NMR (200 MHz) δ 0.04 (6 H, s, CH_3Si), 0.89 (9 H, s, $(CH_3)_3CSi$), 0.97 (6 H, d, $(CH_3)_2CH$, *J* = 6.7 Hz), 2.26 (1 H, d of octet, $CH(CH_3)_2$, *J* = 1.0 (d), 6.6 Hz), 2.42 (1 H, d of quint, $CHCH_2OH$, *J* = 7.7 (d), 5.9 Hz), 3.50–3.70 (4 H, m, CH_2O), 3.81 (3 H, s, OCH_3), 4.53 (2 H, s, CH_2Ar), 4.72 (2 H, s, OCH_2O), 5.32 (1 H, ddd, CH=CHiPr, *J* = 1.0, 7.8, 15.8 Hz), 5.53 (1 H, dd, CH=CHCHCH_2O, *J* = 6.1, 15.8 Hz), 6.84–6.94 (2 H, m, aromatics), 7.20–7.32 (2 H, m, aromatics).

(*R*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-1-[(*tert*-butyldiphenylsilyl)oxy]-5-methylhex-3-ene (83). It was prepared in 89% yield from **79** by the same procedure employed for (*R*)-**81**: R_f = 0.71 (PE/Et_2O (8:2)); $[\alpha]_D$ = +0.49° (*c* 2, $CHCl_3$); ^1H NMR (200 MHz) δ 0.97 (6 H, d, $(CH_3)_2CHC$, *J* = 6.7 Hz), 1.04 (9 H, s, $(CH_3)_3CHSi$), 2.26 (1 H, octet, $CH(CH_3)_2$, *J* = 6.7 Hz), 2.49 (1 H, sextet, $CHCH_2O$, *J* = 6.3 Hz), 3.65 and 3.73 (2 H, AB part of an ABX syst, J_{AB} = 9.4 Hz, J_{AX}, J_{BX} = 5.9, 6.5 Hz), 3.70 (2 H, d, CH_2O, *J* = 5.8 Hz), 4.57 (2 H, s, CH_2Ph), 4.73 (2 H, s, OCH_2O), 5.36 (1 H, ddd, CH=CHiPr, *J* = 1.0, 7.3, 15.6 Hz), 5.52 (1 H, dd, CH=CHCHCH_2O, *J* = 15.6, 6.0 Hz), 7.30–7.45 (11 H, m, aromatics), 7.60–7.73 (4 H, m, aromatics).

(*R*)-(*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-5-methylhex-3-ene (84). It was prepared in 82% yield from **79** by the same procedure employed for (*R*)-**81**: R_f = 0.52 (PE/Et_2O (8:2)); $[\alpha]_D$ = +0.25° (*c* 2, $CHCl_3$); ^1H NMR (200 MHz) δ 0.97 (6 H, d, $(CH_3)_2CHC$, *J* = 6.8 Hz), 1.05 (9 H, s, $(CH_3)_3CHSi$), 2.26 (1 H, octet, $CH(CH_3)_2$, *J* = 6.9 Hz), 2.49 (1 H, sextet, $CHCH_2O$, *J* = 6.5 Hz), 3.64 and 3.72 (2 H, AB part of an ABX syst, J_{AB} = 9.5 Hz, J_{AX}, J_{BX} = 6.0, 6.5 Hz), 3.70 (2 H, d, CH_2O, *J* = 5.7 Hz), 3.80 (3 H, s, OCH_3), 4.50 (2 H, s, CH_2Ar), 4.70 (2 H, s, OCH_2O), 5.36 (1 H, ddd, CH=CHiPr, *J* = 1.0, 7.3, 15.7 Hz), 5.52 (1 H, dd, CH=CHCHCH_2O, *J* = 15.7, 6.0 Hz), 6.83–6.95 (2 H, m, aromatics), 7.20–7.30 (2 H, m, aromatics), 7.30–7.45 (6 H, m, aromatics), 7.60–7.73 (4 H, m, aromatics).

(*S*)-(*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-[[[(*p*-methoxybenzyl)oxy]methoxy]methyl]-5-methylhex-3-ene (84). It was prepared in 84% yield from **77** and $Ph_2tBuSiCl$ by the same procedure employed for (*S*)-**81**: $[\alpha]_D$ = −0.3° (*c* 2, $CHCl_3$).

(*R*)-(*E*)-2-[[[(*p*-Methoxybenzyl)oxy]methoxy]methyl]-1-[(triisopropylsilyl)oxy]-5-methylhex-3-ene (85). It was prepared from **80** in 92% yield by the same procedure used for (*R*)-**81**: R_f = 0.77 (PE/Et_2O (8:2)); $[\alpha]_D$ = +5.7° (*c* 2.23, $CHCl_3$); ^1H NMR (200 MHz) δ 0.97 (6 H, d, $(CH_3)_2CHC$, *J* = 6.7 Hz), 1.00–1.20 (21 H, m, $(CH_3)_2CHSi$), 2.26 (1 H, octet, $CH(CH_3)_2$, *J* = 6.7 Hz), 2.44 (1 H, d of quint, $CHCH_2O$, *J* = 6.1 (quint), 7.8 Hz (d)), 3.61 and 3.69 (2 H, AB part of an ABX syst, J_{AB} = 9.4 Hz, J_{AX}, J_{BX} = 6.0, 6.2 Hz), 3.71 (2 H, d, CH_2O, *J* = 5.8 Hz), 3.81 (3 H, s, OCH_3), 4.53 (2 H, s, CH_2Ar), 4.73 (2 H, s, OCH_2O), 5.36 (1 H, ddd, CH=CHiPr, *J* = 1.0, 7.9, 15.7 Hz), 5.54 (1 H, dd, CH=CHCHCH_2O, *J* = 6.2, 15.7 Hz), 6.83–6.95 (2 H, m, aromatics), 7.22–7.32 (2 H, m, aromatics).

General Procedure for Ozonolysis of Alkenes 81–85, 93, 95, and 98. (*Caution*: ozone is toxic and ozonides are potentially explosive. This reaction must be carried out under a hood and behind a safety shield). A solution of the alkene (3.0 mmol) in MeOH (25 mL) and CH_2Cl_2 (15 mL) was cooled to −78 °C. Ozone was bubbled into the solution until persistence of a grey/blue color. After further bubbling of O_2 for 5 min, Me_2S (2.5 mL) and pyridine (0.020 mL) were added. After 2 min the flask was put under a nitrogen atmosphere, allowed to warm to rt, and stirred for 2 h. Evaporation of the solvent and stripping at 10^{-2} mbar for 2 h afforded crude aldehydes which were not further purified, but used as such at once (or after 1 night in freezer) for further reactions. We have carried out several addition reactions to these aldehydes and from the isolated yields we deduced that these ozonolyses proceed in at least 92% yields.

(*S*)- or (*R*)-2-[[(Benzyloxy)methoxy]methyl]-3-[(*tert*-butyldimethylsilyl)oxy]-1-propanol (91). The crude aldehyde obtained as above described starting from (*S*)-**81**, (*R*)-**81**, (*R*)-**95**, or (*R*)-**98** (0.5 mmol) was dissolved in MeOH (5 mL) and treated with $NaBH_4$ (2.5 mmol). After being stirred at rt for 15 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with AcOEt to give, after evaporation and chromatography, pure **91** (yield = 92% from **81**, 84% from **95**, and 87% from **98**): R_f = 0.36 (PE/Et_2O (6:4)); $[\alpha]_D \simeq 0°$ (*c* 2, $CHCl_3$); ^1H NMR (200 MHz) δ 0.07 (6 H, s, $(CH_3)_2Si$), 0.89 (9 H, s, $(CH_3)_3CSi$), 2.02 (1 H, heptet, $CH(CH_2)_3$, *J* = 5.6 Hz), 2.64 (1 H, t, O*H*, *J* = 5.7 Hz), 3.68 (2 H, d, CH_2O, *J* = 6.2 Hz), 3.73–3.86 (4 H, m, CH_2O), 4.61 (2 H, s, CH_2Ph), 4.76 (2 H, s, OCH_2O), 7.25–7.40 (5 H, m, aromatics).

(*R*)-(*E*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]non-3-en-1-ol (92). It was prepared in 88% yield from **29** by the same procedure employed for preparation of **79**: R_f = 0.43 (PE/Et_2O (8:2)); $[\alpha]_D$ = +2.7° (*c* 2, $CHCl_3$); ^1H NMR (80 MHz) δ 0.90 (3 H, bt, CH_3CH_2), 1.05 (9 H, s, $(CH_3)_3CSi$), 1.20–1.60 (6 H, m, $CH_3(CH_2)_3$), 1.82–2.20 (2 H, m, CH_2CH=CH), 2.20–2.70 (2 H, m, O*H*, *CH*CH=CH), 3.48–4.00 (4 H, m, CH_2O), 5.10–5.80 (2 H, m, *CH*=CH), 7.20–7.47 (6 H, m, aromatics), 7.50–7.81 (4 H, m, aromatics).

(*R*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]non-3-ene (93). It was prepared from **92** in 76% yield by the same procedure used for preparation of (*R*)-**81**: R_f = 0.62 (PE/Et_2O (8:2)); $[\alpha]_D$ = +0.6° (*c* 2, $CHCl_3$); ^1H NMR (80 MHz) δ 0.90 (3 H, bt, CH_3CH_2), 1.05 (9 H, s, $(CH_3)_3CSi$), 1.20–1.60 (6 H, m, $CH_3(CH_2)_3$), 1.70–2.20 (2 H, m, CH_2CH=CH), 2.47 (1 H, sextet, *CH*CH=CH, *J* = 5.7 Hz), 3.69 (4 H, d, CH_2O, *J* = 5.7 Hz), 4.56 (2 H, s, CH_2Ph), 4.72 (2 H, s, OCH_2O), 5.27–5.54 (2 H, m, *CH*=*CH*), 7.20–7.47 (6 H, m, aromatics), 7.50–7.81 (4 H, m, aromatics).

(*R*)-(*E*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]non-3-en-1-ol (94). It was prepared in 93% yield from **29** by the same procedure employed for preparation of **78**: R_f = 0.21 (PE/Et_2O (85:15)); $[\alpha]_D$ = +15.5° (*c* 2, $CHCl_3$); ^1H NMR (200 MHz) δ 0.07 (6 H, s, CH_3Si), 0.88 (3 H, bt, CH_3CH_2), 0.90 (9 H, s, $(CH_3)_3CSi$), 1.15–1.50 (6 H, m, $CH_3(CH_2)_3$), 2.00 (2 H, q, CH_2CH=CH, *J* = 6.6 Hz), 2.38–2.56 (1 H, m, *CH*CH=CH), 2.63 (1 H, dd, O*H*, *J* = 5.2, 6.4 Hz), 3.53–3.86 (4 H, m, CH_2O), 5.23 (1 H, ddt, *CH*=$CHCH_2$, *J* = 1.2 (t), 8.0, 15.6 Hz), 5.57 (1 H, dt, *CH*=CHCH, *J* = 6.6 (t), 15.6 Hz (d)).

(*R*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]non-3-ene (95). It was prepared from **94** in 84% yield by the same procedure used for preparation of (*R*)-**81**: R_f = 0.43 (PE/Et_2O (95:5)); $[\alpha]_D$ = +3.0° (*c* 2.5, $CHCl_3$); ^1H NMR (200 MHz) δ 0.04 (6 H, s, CH_3Si), 0.89 (9 H, s, $(CH_3)_3CSi$), 0.89 (3 H, bt, CH_3CH_2), 1.15–1.50 (6 H, m, $CH_3(CH_2)_3$), 2.01 (2 H, q, CH_2CH=CH, *J* = 6.6 Hz), 2.44 (1 H, sextet, *CH*CH=CH, *J* = 6.5 Hz), 2.63 (1 H, dd, O*H*, *J* = 5.2, 6.4 Hz), 3.61 (2 H, d, CH_2O, *J* = 6.1 Hz), 3.59 and 3.67 (2 H, AB part of an ABX syst, CH_2O, J_{AB} = 9.5, J_{AX}, J_{BX} = 5.9, 7.1 Hz), 4.60 (2 H, s, CH_2Ph), 4.76 (2 H, s, OCH_2O), 5.36 (1 H, dd, *CH*=$CHCH_2$, *J* = 7.8, 15.5 Hz), 5.54 (1 H, dt, *CH*=CHCH, *J* = 6.3 (t), 15.5 Hz (d)), 7.25–7.40 (5 H, m, aromatics).

(*R*)-(*E*)-1-Acetoxy-2-[[(benzyloxy)methoxy]methyl]non-3-ene (96). It was prepared in 76% yield from **29** (see preparation of **76**): R_f = 0.64 (PE/Et_2O (7:3)); $[\alpha]_D$ = +1.5° (*c* 2, $CHCl_3$); ^1H NMR (80 MHz) δ 0.87 (3 H, bt, CH_3CH_2) 1.10–1.50 (6 H, m, $CH_3(CH_2)_3$), 2.02 (3 H, s, CH_3C=O), 2.60 (1 H, sextet, $CHCH_2OAc$, *J* = 6.3 Hz), 3.59 (2 H, d, CH_2OBOM, *J* = 6.0 Hz), 4.11 (2 H, d, CH_2OAc, *J* = 6.3 Hz), 4.58 (2 H, s, CH_2Ph), 4.74 (2 H, s, OCH_2O), 5.20–5.90 (2 H, m, *CH*=CH), 7.33 (5 H, s, aromatics).

(*S*)-(*E*)-2-[[(Benzyloxy)methoxy]methyl]-1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]non-3-ene (93). It was prepared from **96** in 68% overall yield by saponification of the acetyl group (see preparation of **76**) followed by protection with $Ph_2tBuSiCl$ (see preparation of (*S*)-**81**): $[\alpha]_D$ = −0.64° (*c* 2, $CHCl_3$).

(*R*)- or (*S*)-2-[[(Benzyloxy)methoxy]methoxy]-3-[(*tert*-butyldiphenylsilyl)oxy]-1-propanols (97). They were prepared from (*R*)- or (*S*)-**93** in 60% yield by using the same procedure employed for **91**: R_f = 0.11 (PE/Et_2O (7:3)); ^1H NMR (80 MHz)

δ 1.05 (9 H, s, $(CH_3)_3Si$), 2.06 (1 H, heptet, $CHCH_2OH$, J = 5.7 Hz), 2.33 (1 H, t, OH, J = 5.3 Hz), 3.69 (2 H, d, CH_2O, J = 6.3 Hz), 3.78 (2 H, d, CH_2O, J = 5.9 Hz), 3.55–3.90 (2 H, m, CH_2O), 4.54 (2 H, s, CH_2Ph), 4.70 (2 H, s, OCH_2O), 7.15–7.50 (11 H, m, aromatics); 7.50–7.80 (4 H, m, aromatics).

(*R*)-2-[[(Benzyloxy)methoxy]methyl]-3-[(*tert*-butyldimethylsilyl)oxy]propylidenecyclohexane (99). Alcohol **98** was prepared from **32** in 70% yield by the same procedure used for **78**, R_f = 0.33 (PE/Et_2O (8:2)). It was directly protected with BOM-Cl to give (*R*)-**99** in 77% yield using the same procedure employed for preparation of (*R*)-**81**: R_f = 0.45 (PE/Et_2O (9:1)); $[\alpha]_D$ = +0.2° (*c* 1.3 $CHCl_3$); ^1H NMR (200 MHz) δ 0.04 (6 H, s, CH_3Si), 0.89 (9 H, s, $(CH_3)_3CSi$), 1.40–1.63 (6 H, m, ring CH_2), 2.00–2.23 (4 H, m, allylic ring CH_2), 2.74 (1 H, d of quint, CHC-H=C, J = 6.0 (quint), 9.1 Hz (d)), 3.56 (2 H, d, CH_2O, J = 6.0 Hz), 3.54 and 3.65 (2 H, AB part of an ABX syst, CH_2O, J_{AB} = 9.4 Hz, J_{AX}, J_{BX} = 5.8, 6.0 Hz), 4.60 (2 H, s, CH_2Ph), 4.75 (2 H, s, OCH_2O), 5.00 (1 H, bd, CH=C, J = 9.1 Hz), 7.25–7.40 (5 H, m, aromatics).

(*R*)-2-[[(Benzyloxy)methoxy]methyl]-1-[(*tert*-butyldiphenylsilyl)oxy]propane (100). (a). A solution of alcohol (*R*)-**97** (63 mg, 0.136 mmol) in dry CH_2Cl_2 (5 mL) was treated with Et_3N (51 μL, 0.366 mmol), DMAP (9 mg, 0.074 mmol), and TsCl (69 mg, 0.362 mmol). After being stirred at rt for 3 days, the reaction was quenched with NH_4Cl (30 mg), diluted with H_2O and extracted with Et_2O to give, after evaporation and chromatography, pure tosylate of **97** (75 mg, 89%): R_f = 0.42 (PE/Et_2O (7:3)), 0.19 (PE/Et_2O (8:2)); ^1H NMR (80 MHz) δ 0.98 (9 H, s, $(CH_3)_3CSi$), 2.16 (1 H, heptet, $CHCH_2OTs$, J = 5.7 Hz), 2.39 (3 H, s, CH_3 of tolyl group), 3.56 (2 H, d, CH_2O, J = 6.3 Hz), 3.64 (2 H, d, CH_2O, J = 6.5 Hz), 4.18 (2 H, d, CH_2OTs, J = 5.9 Hz), 4.47 (2 H, s, CH_2Ph), 4.60 (2 H, s, oCH_2O), 7.20–7.85 (19 H, m, aromatics). This tosylate (0.121 mmol) was taken up in DMSO (6 mL) and treated with $NaBH_4$ (45 mg, 1.19 mmol). The solution was stirred for 1 h at rt, 5 h at 60 °C, and overnight at rt. Quenching with diluted NH_4Cl, extraction with Et_2O, evaporation, and chromatography gave pure (*R*)-**100** (32 mg, 58%): R_f = 0.60 (PE/Et_2O (8:2)); $[\alpha]_D$ = +6.0° (*c* 0.65, $CHCl_3$); ^1H NMR (80 MHz) δ 0.97 (3 H, d, CH_3CH, J = 7.4 Hz), 1.05 (9 H, s, $(CH_3)_3CSi$), 1.75–2.22 (1 H, m, $CHCH_3$, mc = 1.99 ppm), 3.48 (2 H, d, CH_2O, J = 5.4 Hz), 3.58 (2 H, d, CH_2O, J = 5.7 Hz), 4.54 (2 H, s, CH_2Ph), 4.70 (2 H, s, OCH_2O), 7.50–7.80 (4 H, m, aromatics).

(b). A solution of (*R*)-2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-1-propanol, prepared from (*S*)-**101**[41] (198 mg, 0.603 mmol) in dry CH_2Cl_2 (20 mL) was treated, at rt, with $EtN(iPr)_2$ (0.41 mL, 2.39 mmol) and $BnOCH_2Cl$ (0.170 mL, 1.22 mmol). After stirred overnight at rt, the mixture was worked up as usual (see preparation of **76**) to give pure (*R*)-**100** (184 mg, 68%): $[\alpha]_D$ = +6.0° (*c* 2, $CHCl_3$).

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Registry No. **4**, 126-11-4; **4** triacetate, 7344-23-2; **5**, 86629-63-2; **6**, 138435-86-6; **7**, 138435-87-7; **8**, 138435-88-8; **9**, 138435-89-9; (*R*)-**11**, 138435-90-2; (*S*)-**11**, 138435-91-3; (*R*)-**12**, 138435-92-4; (*S*)-**12**, 138435-93-5; **13**, 4728-14-7; **14**, 138435-94-6; **15**, 138435-95-7; **16**, 138435-96-8; **17**, 51615-31-7; **18**, 51615-30-6; **19**, 18795-86-3; **20**, 13592-76-2; **21**, 138435-97-9; **22**, 138435-98-0; **23**, 96185-02-3; **24**, 71310-20-8; **25**, 133490-80-9; **26**, 133490-81-0; **27**, 138435-99-1; **28**, 133490-88-7; **29**, 133575-93-6; **30**, 133575-94-7; **31**, 138436-00-7; **32**, 133490-93-4; **33**, 138458-94-3; **34**, 138436-01-8; **35**, 96185-01-2; **36**, 77192-46-2; **37**, 133490-82-1; **38**, 133490-83-2; **39**, 110230-66-5; **40**, 628-71-7; **41**, 598-23-2; **42**, 627-19-0; **43**, 138436-02-9; **43** mesylate, 138436-03-0; **44**, 138436-04-1; **45**, 138436-05-2; **46**, 138436-06-3; **47**, 138436-07-4; **48**, 138436-08-5; **49**, 133490-84-3; **50**, 133490-85-4; **51**, 138436-09-6; **52**, 133490-86-5; **53**, 133490-87-6; **54**, 138436-10-9; **55**, 133490-89-8; **56**, 133490-90-1; **57**, 138513-51-6; **58**, 133490-91-2; **59**, 133490-92-3; **60**, 138436-11-0; **61**, 133575-95-8; **62**, 133575-96-9; **63**, 138436-12-1; **64**, 5468-79-1; **65**, 25462-27-5; **66**, 110230-67-6; **67**, 138436-13-2; **68**, 138436-14-3; **69**, 138436-15-4; **70**, 138436-16-5; **71**, 138436-17-6; **72**, 138436-18-7; **74**, 105409-38-9; **76**, 138513-52-7; **77**, 138436-19-8; **78**, 138513-53-8; **79**, 138436-20-1; **80**, 138436-21-2; **80** acetate, 138436-22-3; (*R*)-**81**, 138513-54-9; (*S*)-**81**, 138513-55-0; (*R*)-**82**, 138436-23-4; (*R*)-**83**, 138436-24-5; (*R*)-**84**, 138436-25-6; (*S*)-**84**, 138436-26-7; (*R*)-**85**, 138436-27-8; (*R*)-**86**, 133377-92-1; (*S*)-**86**, 135218-62-1; (*R*)-**87**, 138436-28-9; (*R*)-**88**, 138436-29-0; (*R*)-**89**, 138436-30-3; (*S*)-**89**, 138436-31-4; (*R*)-**90**, 138436-32-5; (*R*)-**91**, 138436-33-6; (*S*)-**91**, 138436-34-7; (*R*)-**92**, 138436-35-8; (*R*)-**93**, 138513-56-1; (*S*)-**93**, 138513-57-2; (*R*)-**94**, 138436-36-9; (*R*)-**95**, 138436-37-0; (*R*)-**96**, 138436-38-1; (*R*)-**97**, 122535-98-2; (*R*)-**97** tosylate, 138436-39-2; (*S*)-**97**, 138436-40-5; (*R*)-**98**, 138436-41-6; (*R*)-**99**, 138436-42-7; (*R*)-**100**, 122535-99-3; (*S*)-**101**, 92817-88-4; $BnOCH_2Cl$, 3587-60-8; *i*-Pr_3SiOTf, 80522-42-5; $PMBOCH_2Cl$, 64610-11-3; (*R*)-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1-propanol, 95514-04-8; diethyl malonate, 105-53-3; heptanal, 111-71-7; isovaleraldehyde, 590-86-3; valeraldehyde, 110-62-3; cyclohexanecarboxaldehyde, 2043-61-0; 1,3-diacetoxyacetone, 6946-10-7; *cis*-tetrahydro-2,5-furandimethanol acetate, 119873-51-7; *cis*-3,4-bis(acetoxymethyl)cyclopentanone, 111050-92-1; 4-acetoxy-1,2-cyalopentanedimethanol diacetate, 138436-43-8; (1*S*-*trans*)-3-cyclopentene-1,2-dimethanol diacetate, 138513-58-3; β,2,2,5-tetramethyl-1,3-dioxane-4-ethanol acetate, 138513-59-4; 2-(acetoxymethyl)-4-penten-1-ol acetate, 63127-61-7; lipase, 9001-62-1; 7,8-bis(acetoxymethyl)-1,4-dioxaspiro[4.4]nonane, 111050-93-2.

Supplementary Material Available: Elemental analyses for compounds **5–9**, **11**, **12**, **14**, **16**, **17**, **21**, **25**, **92–96**; ^1H NMR spectra for compounds **18–20**, **22–24**, **26–32**, **37–39**, **43–46**, **49–63**, **76–85**, **91**, **97**, **99**, **100**; GC conditions for the estimation of purity of compounds **18–20**, **22–26**, **29**, **37**, **38**, **46**, **49–55**, **60**, **63** (52 pages). Ordering information is given on any current masthead page.