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Enzymatic Approach to Enantiomerically Pure 5-Alken-2,4-diols and 4-Hydroxy-5-alken-2-ones: Application to the Synthesis of Chiral Synthons

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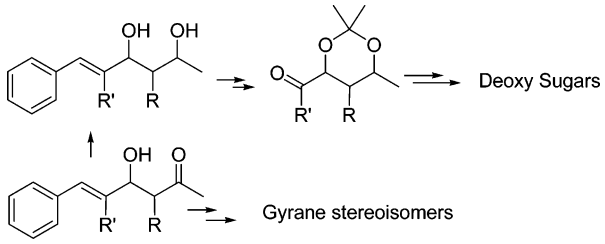
Received March 16, 2006



Enantiomerically pure 1,3-diols **1**−**3** were obtained by a chemoenzymatic approach (lipase PS from Burkholderia cepacia). These diols were converted into useful chiral synthons, which could be considered homologues of glyceraldehyde and glyceric acid acetonides. Applications of these synthons to the de novo synthesis of sugars and preparation of conagenin carboxylic moiety were shown. Hydroxy ketone **4** was chosen as a model system for another synthetic evolution: it was obtained in enantiomerically pure form by enzymatic resolution and converted into chiral tetrahydropyranes, such as the stereoisomers of the commercial fragrance Gyrane.

Introduction

According to the annual survey on chiral chemistry published in *Chemical and Engineering News* in 2004[1] the global sales of single-enantiomer compounds are expected to reach $14.94 billion by the end of 2009, growing annually by 11.4%. By 2009, the share of the market realized through traditional technology would drop to 41%, the share of chemocatalysis would reach 36%, and the share of biocatalysis would reach 22%. Demand for enantiomerically pure chiral compounds is progressively rising, primarily for use in pharmaceuticals but also in three other sectors: flavor and fragrance chemicals, agricultural chemicals, and specialty materials.

One strategy employed to speed up the process of "chiral switch", from both an economical and a chemical point of view, is to optimize enantiomerically pure chiral synthons in order to kill two birds with one stone. For example, C_3 chirons showing a stereocenter in position 2, such as protected glycerol, glyceraldehydes, and glyceric acid derivatives, are well-known versatile intermediates amenable for a variety of synthetic transformations.

We now report on the enzyme-mediated preparation of enantiomerically enriched stereoisomers of diols **1**−**3**, obtained by reduction of the corresponding aldol derivatives **4**−**6**. We will show that diols **1**−**3** are useful chiral synthons: a carbonyl functionality can be generated by ozonolysis of the double bond to afford the protected chiral dihydroxy carbonyl derivatives **7**−**9**. Interesting applications of these chirons to the de novo synthesis of deoxy sugars and preparation of conagenin carboxylic moiety will be described.

We chose hydroxy ketone **4** as a model compound to show another synthetic development: (*R*)-**4**, obtained in enantiopure form by lipase-catalyzed resolution, can be employed to prepare chiral tetrahydropyrane stereoisomers **10**.

Results and Discussion

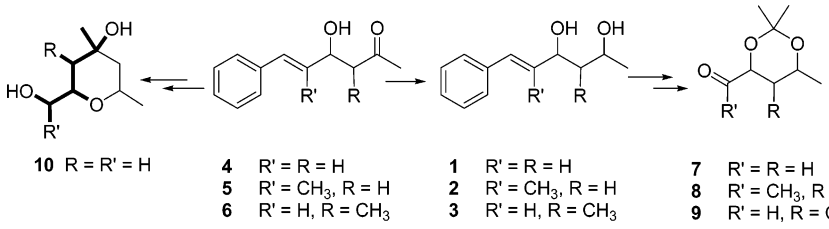
A. Lipase-Catalyzed Resolution of Diols 1−3. The 1,3-diol moiety occurs frequently in natural compounds.[2] The synthetic

(1) Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (June 14), 47.

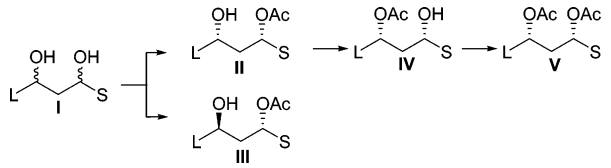
(2) 1,3-Diols: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (b) Schneider, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1375. (c) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635.

10.1021/jo060581w CCC: $33.50
Published on Web 06/13/2006

CHART 1

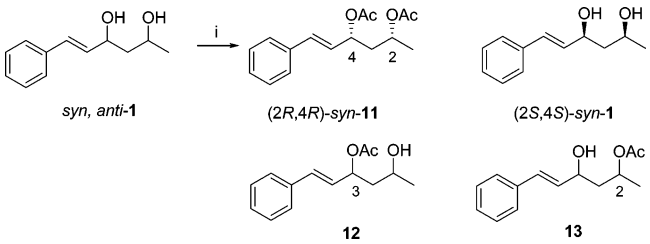


SCHEME 1[a]



[a] Redrawn from ref 7.

SCHEME 2[a]



[a] (i) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography.

strategies to *syn*- and *anti*-1,3-diols include the following: (a) reduction of β-hydroxy ketones (diastereoselection can be obtained by suitable choice of the reducing agent),[3] (b) Tishchenko reaction,[4] and (c) stereoselective reduction of 1,3-diketone.[5] The latest developments in this field have been summarized by Müller et al. in a recent review.[6]

Study of the enzyme-mediated transesterification of 1,3-diols is a challenge in synthetic organic chemistry. While our work was in progress an interesting paper by Bäckwall appeared in *PNAS*. Bäckwall reported[7] on the one-pot synthesis of enantiomerically pure *syn*-1,3-diacetates from racemic syn/anti mixtures of 1,3-diols by dynamic kinetic asymmetric transformation (Scheme 1). Lipase-mediated acetylation of unsymmetrical 1,3-diols **I**, with a large and small group, combined with a ruthenium epimerization catalyst would give a mixture of *R*-monoacetates **II** and **III**.

According to Bäckwall, monoacetate **II** can undergo fast *syn*-acyl migration to give **IV**, whereas the corresponding *anti*-acyl migration from **III** is slow. Because of the ruthenium-catalyzed epimerization of **III** to **II**, almost all of the monoacetate will be converted into **IV** via the *syn*-acyl transfer. The released *R*-alcohol in **IV** will finally undergo fast enzymatic acylation to give enantiomerically pure diacetate **V**. According to this procedure several differently substituted unsymmetrical, acyclic *syn*-1,3-diacetates were obtained in yields up to 73% (yields determined by GC or HPLC) with excellent enantioselectivities (>99%) and good diastereomeric ratios (>90% syn).

We prepared diols **1**−**3** by $NaBH_4$ reduction of the corresponding hydroxy ketones **4**−**6**, prepared by classical aldol condensation. Interestingly enough, high regioselectivity (95%) was obtained in the reaction of cinnamaldehyde with methyl ethyl ketone using 10% NaOH in methanol solution.

We performed a preliminary investigation of the lipase PS-mediated acetylation of the 1:1 syn/anti mixture of diol **1** in *tert*-butyl methyl ether in the presence of vinyl acetate (Scheme 2). By assuming that lipase PS promotes the acetylation of stereogenic centers of well-defined configuration, the syn diastereoisomer was expected to give a diacetate and diol of opposite configuration while the anti diastereoisomer should give two regioisomeric monoacetates of opposite configuration.

After 7 days the following products could be isolated (Scheme 2): (2*R*,4*R*)-*syn*-**11** (de > 99%, ee = 96% of the corresponding diol), (2*S*,4*S*)-*syn*-**1** (de > 99%, ee = 97%), *anti*-**12** (impure, 7% of *syn*-**12** and 10% of *syn*-**13**), *anti*-**13** (impure, 10% of *syn*-**13**). Neither diacetate *anti*-**11** nor diol *anti*-**1** could be isolated. The absolute stereochemistry of *syn*-**11** and *syn*-**1** was tentatively assigned on the basis of a known preference of lipase PS for (*R*) stereocenters. The two regioisomeric anti monoacetates could not be isolated as pure compounds; thus, no conclusion could be drawn on their optical purity and absolute configuration. We chose lipase PS as a catalyst because we had experienced its efficiency in the transesterification of allylic alcohols.[8a,b]

We then decided to exploit the lipase PS acetylation of the parent hydroxy ketone **4**, which we had already experimented[8c,d] within a work devoted to the chemistry of fragrances. The data

(3) *Syn*-reduction, see for example: (a) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233. (b) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. S.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803. (c) Hoveyda, A. H.; Evans, D. A. *J. Org. Chem*. **1990**, *55*, 5190. *Anti*-reduction, see for example: (a) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem*. **1997**, *62*, 3409. (b) Hoveyda, A. H.; Evans, D. A. *J. Am. Chem. Soc*. **1990**, *112*, 6447. (c) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761.

(4) (a) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem*. **1997**, *62*, 5674. (b) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem*. **1997**, *62*, 3409. (c) Marwald, R.; Cortisella, B. *Synthesis* **1996**, 1087. (d) Evans, D. A.; Hoveyda, H. A. *J. Am. Chem. Soc*. **1990**, *112*, 6447.

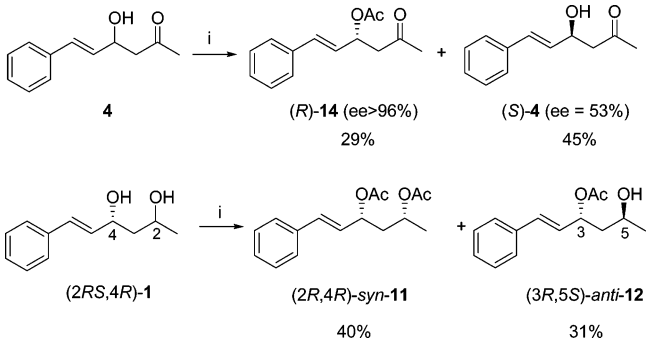
(5) Reduction of diketones. By catalytic hydrogenation: (a) Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 4041. (b) Brunner, H.; Terfort, A. *Tetrahedron: Asymmetry* **1995**, *6*, 919. By enzymatic methods: (c) Ikeda, H.; Sato, E.; Sugai, T.; Ohta, H. *Tetrahedron* **1996**, *52*, 8113. (d) Takeshita, M.; Miura, M.; Unuma, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2901. (e) Chenevert, R.; Thiboutot, S. *Can. J. Chem*. **1986**, *64*, 1599. With metallic hydrides: for example, see: (f) Bonini, C.; Righi, G.; Rossi, L. *Tetrahedron* **1992**, *48*, 9801. (g) Barluenga, J.; Resa, J.; Olano, B. *J. Org. Chem.* **1987**, *52*, 1425. (h) Yamada, F.; Horie, T.; Kawai, M.; Yamamura, H. Araki, S. *Tetrahedron* **1997**, *53*, 15685. (i) Bartoli, G.; Bosco, M.; Bellocci, M. C.; Dal pozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* **2000**, *2*, 45−47.

(6) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557−588.

(7) Edin, M.; Steinreiber, J.; Bäckwall, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5761−5766.

(8) (a) Brenna, E.; Fuganti, C.; Fronza, G.; Malpezzi, L.; Righetti, A.; Serra, S. *Helv. Chim. Acta* **1999**, *82*, 2246−2259. (b) Brenna, E.; Fuganti, C.; Grasselli, P.; Serra, S. *Eur. J. Org. Chem.* **2001**, 1349−1357. (c) Abate A.; Brenna, E.; Fuganti, C.; Serra, S. *Flavour Fragrance J.* **2004**, *19*, 382−393. (d) Abate, A.; Brenna, E.; Fronza, G.; Fuganti, C.; Gatti, F. G.; Serra, S. Zardoni, E. *Helv. Chim. Acta* **2004**, *87*, 765−780.

SCHEME 3[a]



[a] (i) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography.

of the transesterification was also confirmed by the work of Joly and Nair.[9] These authors determined the enantiomeric purity by HPLC analysis and assigned the absolute stereochemistry to hydroxy ketone **4** by means of chemical correlation.[9] Lipase PS transesterification of hydroxy ketone **4** was rather slow but afforded the corresponding acetate derivative (*R*)-**14** with high enantiomeric excess (ee > 96%) (Scheme 3).

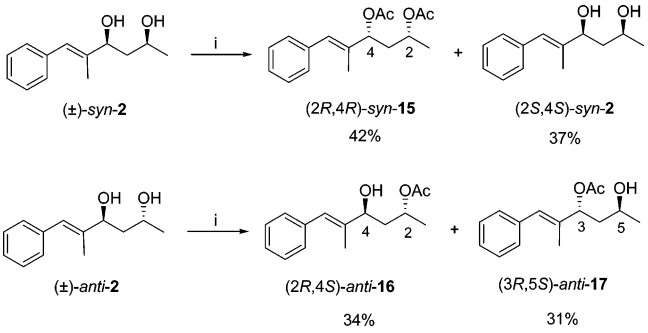
Reduction and saponification of (*R*)-**14** gave a 1:1 mixture of the two diastereoisomeric diols (2*R*,4*R*)-*syn*-**1** and (2*S*,4*R*)-*anti*-**1**, which was submitted to lipase PS-mediated acetylation in *tert*-butyl methyl ether, in the presence of vinyl acetate (Scheme 3). After 7 days we could recover the syn stereoisomer as a diacetate, (2*R*,4*R*)-*syn*-**11** (de > 99%, ee = 96% of the corresponding diol), and the anti stereoisomer as a monoacetate, (3*R*,5*S*)-*anti*-**11** (de > 99%, ee = 96% of the corresponding diol). (The numbering seems to be deceptive but it is that obtained by applying IUPAC rules of nomenclature.) No unreacted diol was recovered. We could not discriminate whether formation of the syn diacetate did or did not involve an intermediate acyl migration. Anyway, the result was a complete diastereoselectivity in the formation of (2*R*,4*R*)-*syn*-**11**. As for the anti stereoisomer, no anti diacetate could be found, only trace amounts of monoacetate (2*S*,4*R*)-*anti*-**13**, probably generated by an acyl migration of (3*R*,5*S*)-*anti*-**12**. The configuration of **4** was known,[9] and the relative configuration of diols **1** was established by comparison with the proton spectra of the same diols reported in the literature[10] and confirmed by the ^{1}H NMR spectra of the corresponding acetonides (see Experimental Section).

A great preference for the acetylation of *R* stereogenic centers was confirmed. We could verify that if the anti diol was not epimerized, it did not interfere in the acetylation of the syn diastereoisomer and both of them could be recovered as single enantiomers with de > 99%.

According to our approach, starting from (*R*)-**4** it is possible to recover enantiomerically pure (2*R*,4*R*)-*syn*- and (2*S*,4*R*)-*anti*-**1** as single diastereoisomers, while both enantiomers of *syn*-**1** can be obtained using a racemic mixture of *syn*- and *anti*-**1** as a substrate for lipase-catalyzed acetylation.

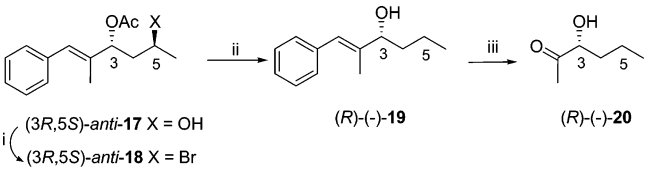
As for diol **2**, the two racemic diastereoisomers could be separated by column chromatography, and they were submitted separately to lipase PS transesterification. After 7 days (±)-*syn*-**2** gave diacetate (2*R*,4*R*)-*syn*-**15** (ee > 99%, by HPLC of the corresponding diol) and diol (2*S*,4*S*)-*syn*-**2** (ee > 99% by HPLC) (Scheme 4).

SCHEME 4[a]



[a] (i) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography.

SCHEME 5[a]



[a] (i) CBr_4, PPh_3, CH_2Cl_2. (ii) Redal in Toluene. (iii) O_3, CH_2Cl_2/MeOH 2/1, then PPh_3.

Biocatalyzed acetylation of (±)-*anti*-**2** afforded, after a 7 day reaction time, two regioisomeric monoacetates, (2*R*,4*S*)-*anti*-**16** and (3*R*,5*S*)-*anti*-**17**, which could be separated by column chromatography. When (2*R*,4*S*)-*anti*-**16** and (3*R*,5*S*)-*anti*-**17** were hydrolyzed, two enantiomeric diols were obtained, showing, respectively $[\alpha]_D = -32.8$ ($c = 0.86$, $CHCl_3$) and +30.6 ($c = 0.96$, $CHCl_3$).

The relative configuration of the derivatives of this series was assigned on the basis of the ^{1}H NMR spectra of the corresponding acetonides (see Experimental Section) by comparison with those derived from *syn*- and *anti*-**1**.

The absolute configuration of the anti monoacetates and their enantiomeric purity were established by chemical correlation according to the sequence reported in Scheme 5. (3*R*,5*S*)-*anti*-**17** was treated with CBr_4 and PPh_3 in CH_2Cl_2. The crude reaction product **18** was reduced to alcohol (−)-**19** by reaction with Redal in toluene solution. Alcohol (−)-**19** was converted into hydroxy ketone (*R*)-(−)-**20**[11] (optical purity = 92%) by treatment with ozone followed by PPh_3 quenching.

The absolute stereochemistry of syn diacetate and unreacted syn diol was tentatively assigned by analogy. All four stereoisomers of diol **2** were obtained in enantiomerically pure form.

As for diol **3**, we had in our hands a hydroxy ketone precursor **6** which was obtained as a 1:2 mixture of syn and anti stereoisomers by aldol condensation of cinnamaldehyde and ethyl methyl ketone. Less than 5% (NMR) of the regioisomer 5-hydroxy-7-phenylhept-6-en-3-one was detected. Reduction and column chromatography afforded the following products: (a) a 1:1 mixture of (±)-*syn*,*syn*-**3** and (±)-*syn*,*anti*-**3**; (b) (±)-*anti*,-*syn*-**3** (de > 99%); (c) (±)-*anti*,*anti*-**3** (de > 99%). The relative configuration of *anti*,*anti*-**3** was established by X-ray diffraction.

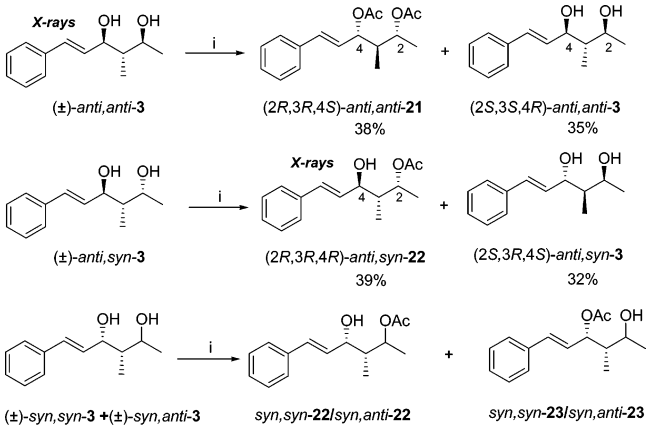
Diol (±)-*anti*,*anti*-**3** was submitted to lipase PS acetylation (Scheme 6) in the usual conditions to afford diacetate (2*R*,3*R*,4*S*)-

(9) Joly, S.; Nair, M. S. *J. Mol. Catal. B: Enzym.* **2003**, *22*, 151.

(10) For *anti*-**1**: Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172−2173. For *syn*- and *anti*-**1**: Aprile, C.; Gruttadauria, M.; Lo Meo, P.; Noto, R. *Heterocycles* **2001**, *57*, 293−305.

(11) Schröder, F.; Fettköther, R.; Noldt, U.; Dettner, K.; König, W. A.; Franche, W. *Liebigs Ann. Chem.* **1994**, 1211−1218.

SCHEME 6[a]



[a] (i) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography.

anti,*anti*-**21** (ee = 97%, HPLC of the corresponding diol) and (2*S*,3*S*,4*R*)-*anti*,*anti*-**3** (ee = 97%, HPLC).

Lipase PS treatment of diol (±)-*anti*,*syn*-**3** led to isolate the following products by column chromatography: monoacetate (2*R*,3*R*,4*R*)-*anti*,*syn*-**22** (ee = 95%, HPLC of the corresponding diol) and (2*S*,3*R*,4*S*)-*anti*,*syn*-**3** (ee = 96%, HPLC). A tiny amount (3%) of regioisomeric monoacetate *anti*,*syn*-**23**, which was found to be racemic by HPLC of the corresponding diol, was obtained, probably by acyl migration. The relative configuration of (2*R*,3*R*,4*R*)-*anti*,*syn*-**22** was established by X-ray diffraction analysis.

When the 1:1 mixture of (±)-*syn*,*syn*-**3** and (±)-*syn*,*anti*-**3** was submitted to enzyme-mediated transesterification, it was possible to obtain a 1:1 mixture of monoacetates *syn*,*syn*-**22** and *syn*,*anti*-**22** and 1:1 mixture of regioisomers *syn*,*syn*-**23** and *syn*,-*anti*-**23** by column chromatography. Formation of both regioisomeric monoacetates of *syn*,*anti*-**3** was probably due to acetyl shift.

We also experimented a strategy starting from resolution of hydroxy ketone **4**. The 2:1 mixture of hydroxy ketones *anti*- and *syn*-**6** was treated with lipase PS in the usual conditions. After 7 days column chromatography afforded as the first eluted fraction a 4:1 mixture of (3*S*,4*S*)-*anti*-**24** and (3*S*,4*R*)-*syn*-**24**. From this mixture acetoxy ketone (3*S*,4*S*)-*anti*-**24** separated as a white solid by treatment with hexane. The relative configuration of *anti*-**24** was established by X-ray diffraction analysis, and the absolute stereochemistry was assigned by analogy. Upon $NaBH_4$ reduction and saponification compound (3*S*,4*S*)-*anti*-**24** afforded a 1:1 mixture of (2*R*,3*R*,4*S*)-*syn*,*syn*-**3** and (2*R*,3*R*,4*S*)-*syn*,*syn*-**3**, which could be separated by column chromatography.

Our chemoenzymatic approach allowed us to prepare both enantiomers of diols *anti*,*anti*-**3** and diol *anti*,*syn*-**3** and selectively obtain their (4*S*)-stereoisomers by lipase-mediated acetylation of the corresponding hydroxy ketone.

The X-ray structures of (±)-*anti*,*anti*-**3** (A), (2*R*,3*R*,4*R*)-*anti*,-*syn*-**22** (B), and (3*S*,4*S*)-anti-**24** (C**)** are reported in Figure 1. The configurations of the stereogenic centers are well defined by the torsion angles reported in Table 1, while some aspects of molecular geometries are illustrated by the dihedral angles reported in Table 2.

The crystal structure of (±)-*anti*,*anti*-**3** reveals the presence of an intramolecular hydrogen bonding between the two OH groups (O1···O2 = 2.592(6) Å, H1O···O2 = 1.87(4) Å, O1−H1O···O2 = 146.(2)°) that yields a six-membered pseudo ring (O1−H1O ···O2−C4−C3−C2) showing a distorted chair conformation.

B. Glyceraldehyde Homologues. Once having reached the stereochemical control on the 1,3-diol stereocenters, we submitted the double bond to oxidative cleavage to create the carbonylic function as anticipated in Chart 1. A recent report by Trost et al.[12] presenting S,O-acetals as novel "chiral aldehyde" equivalents showed the importance of gaining access to chiral functionalized carbonyl derivatives.

Enantiomerically pure diols (2*R*,4*R*)-*syn*-**1**, (2*S*,4*R*)-*anti*-**1**, (2*R*,4*R*)-*syn*-**2**, (2*R*,4*S*)-*anti*-**2**, (2*S*,3*S*,4*R*)-*anti*,*anti*-**3**, and (2*R*,3*S*,4*R*)-*anti*,*syn*-**3** were treated with dimethoxypropane in acetone in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate to afford the corresponding acetonides (Chart 2).

The acetonides **25**−**27** were treated with ozone in methylene chloride/methanol 2:1 solution followed by PPh_3 quenching. Column chromatography allowed us to isolate carbonyl derivatives **7**-**9** (Chart 3). Ozonization of (4*S*,6*R*)-*anti*-**25** was rather troublesome. We performed it in methylene chloride/methanol 2/1 solution and quenched it with either PPh_3 or $(CH_3)_2S$. We obtained invariably the same result: when the temperature of the ozonolysis mixture was allowed to rise to room temperature aldehyde *anti*-**7** gave a rearrangement to the methyl deoxy glycoside **28** with loss of the acetonide protection.

Carbonyl compounds **7**−**9** can be considered homologues of glyceraldehyde acetonides **29** and of protected aldehydes **30**,[13] representing a complete series from C_3 to C_6 chirons with fixed configuration of the stereogenic centers (Chart 3).

C. De Novo Synthesis of Deoxy Sugars. The rapid development of glycobiology and carbohydrate-based pharmaceuticals has prompted research in the field of natural and nonnatural carbohydrate synthesis.[14] The approach based on the de novo synthesis of carbohydrates is of great relevance.[15]

Recently, synthetic sequences based on aldol condensation have been reported. MacMillan et al.[16] disclosed a 'two-step' synthesis of aldohexoses consisting of a proline-catalyzed aldol reaction between α-oxygenated aldehydes followed by a Mukaiyama−aldol reaction to generate the carbohydrate. Cordova et al.[17] and Enders et al.[18] proposed their own independent routes based on the proline-catalyzed aldol reaction of suitable dihydroxyacetone derivatives with several aldehydes.

Another recent approach is based on dihydroxylation of double bonds. Galacto sugars and deoxy sugars have been obtained via iterative dihydroxylation of dienoates.[19] Racemic mono- and dihydroxylated furanoses, pyranoses, and oxepanose

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(13) Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.
(14) In *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P., Bertozzi, C., Eds.; Marcel Dekker: New York, 2001.
(15) (a) Ogawa, T. *Chem. Soc. Rev.* **1994**, *23*, 397−407. (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380−1520. (c) Hanessian, S. *Preparative Carbohydrate Chemistry*; Marcel Dekker: New York, 1997. (d) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. *J. Chem. Rev.***1996**, *96*, 1195−1220.
(16) (a) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152−2154. (b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752−1755.
(17) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343−1345. Ibrahem, I.; Zou, W.; Xu, Y.; Cordova A. *Adv. Synth. Catal.* **2006**, *348*, 211−222.
(18) Enders, D.; Grondal, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210−1212. Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329−337.
(19) Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745−748.

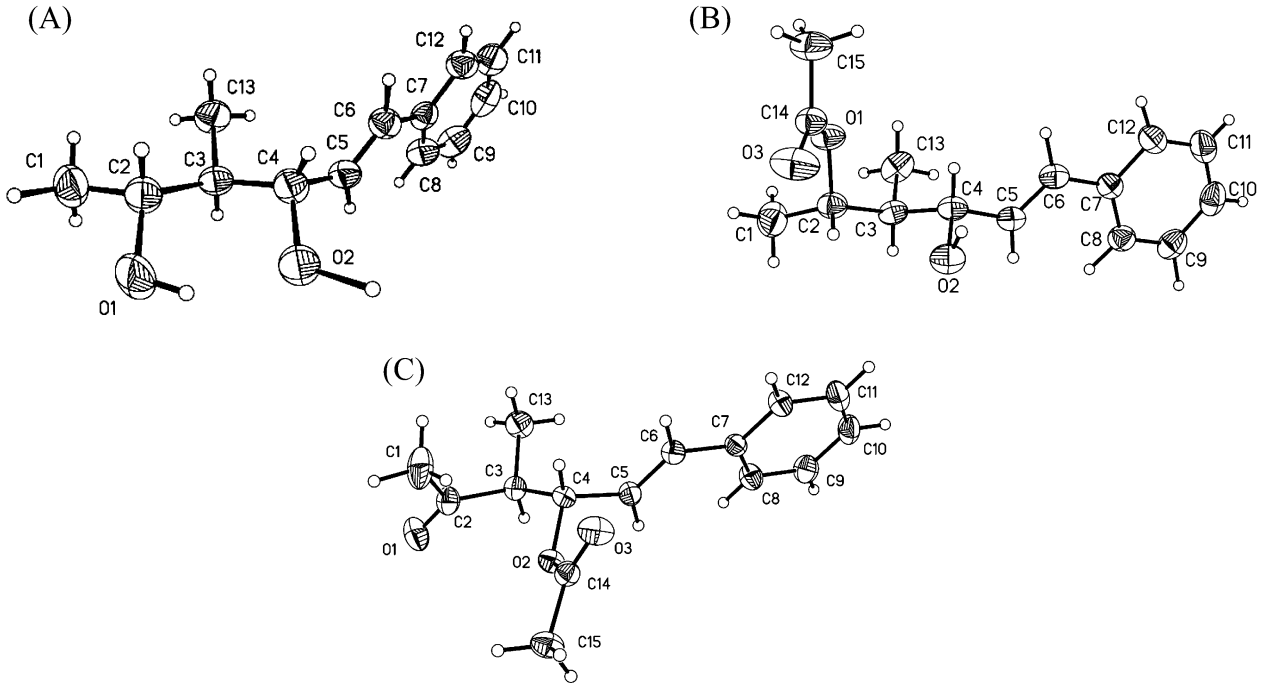


FIGURE 1. X-ray structures of *anti*,*anti*-**3** (A), *anti*,*syn*-**22** (B), and *anti*-**24** (C).

TABLE 1. Selected Torsion Angles

torsion angles (deg)	*anti*,*anti*-**3**	*anti*,*syn*-**22**	*anti*-**24**
O1−C2−C3−C13	175.9(4)	54.9(4)	104.1(4)
C1−C2−C3−C13	49.2(6)	−64.9(4)	−73.9(5)
C13−C3−C4−O2	−174.6(4)	−56.4(3)	174.5(3)
C13−C3−C4−C5	−51.3(5)	57.1(3)	−65.0(4)
C1−C2−C3−C4	177.6(4)	170.3(3)	50.4(5)
C2−C3−C4−C5	179.6(4)	−176.5(3)	171.4(3)
C3−C4−C5−C6	111.5(5)	−115.8(4)	121.3(3)
C4−C5−C6−C7	−177.0(4)	−176.1(3)	−177.6(3)

TABLE 2. Dihedral Angles (deg) between Least-Squares Planes

plane−plane	*anti*,*anti*-**3**	*anti*,*syn*-**22**	*anti*-**24**
Π(C4/C7)-Π(C6/C12)	4.9	6.6	8.9
Π(C1/C5)-Π(C4/C7)	69.2	60.2	38.6
Π(C1/C5)-Π(C6/C12)	64.3	54.3	29.9

to be eventually employed in the preparation of natural product analogue libraries have been recently prepared involving dihydroxylation as a key step.[20]

Our synthetic approach led to the preparation of single enantiomers of carbonyl derivatives **7**−**9** which are themselves deoxy sugars, namely **7** and **9** are protected dideoxyaldopentoses and **8** are protected trideoxyketohexoses. Furthermore, to show the synthetic potentiality of these compounds as chiral synthons, we prepared a trideoxyaldohexose and dideoxyaldohexose starting from (4*R*,6*R*)-*syn*-**7**.

(4*R*,6*R*)-*syn*-**7** was reduced with $NaBH_4$ to give alcohol (4*R*,6*R*)-*syn*-**31** (Scheme 8), which was converted into nitrile (4*R*,6*R*)-*syn*-**32** via tosylate and cyanide displacement.

The nitrile moiety was reduced with diisobutylaluminum hydride at −10 °C, and aldehyde (4*R*,6*R*)-*syn*-**33** was recovered at the end of the sequence. This aldehyde had been used as an intermediate in the synthesis of (−)-*endo*-dimethyl-1,3-dioxa-2,9-bicyclo[3.3.1]nonane,[21] a biologically active substance

CHART 2

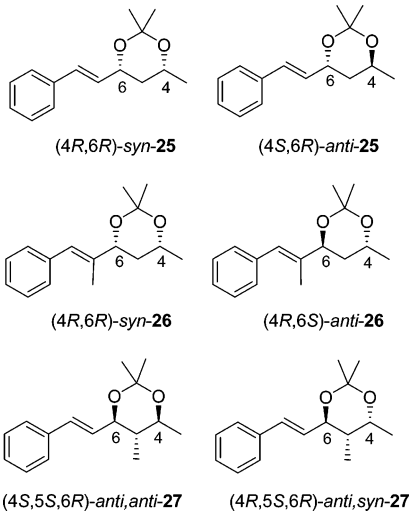
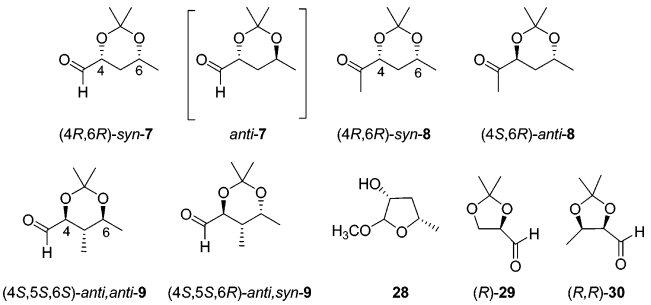


CHART 3



(20) Yu, X. M.; Han, H.; Blagg, B. S. J. *J. Org. Chem.* **2005**, *70*, 5599−5605.

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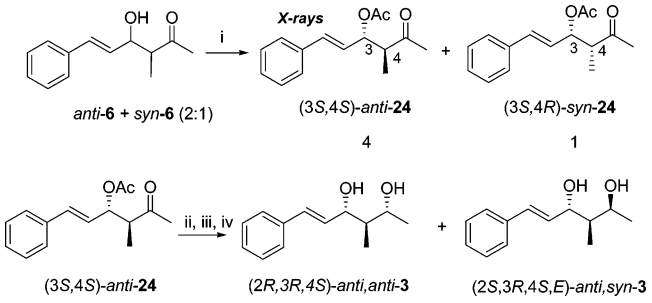
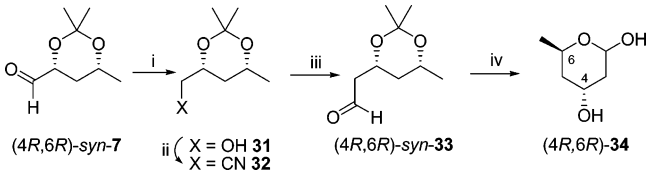
SCHEME 7[a]



[a] (i) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography. (ii) $NaBH_4$, CH_2Cl_2/MeOH 2/1. (iii) KOH, MeOH. (iv) Column chromatography.

SCHEME 8[a]



[a] (i) $NaBH_4$ in CH_2Cl_2−MeOH. (ii) *p*-Toluensulfonyl chloride in pyridine; NaCN in DMSO. (iii) DIBAl, toluene. (iv) THF−H_2O, AcOH, HCl conc. cat.

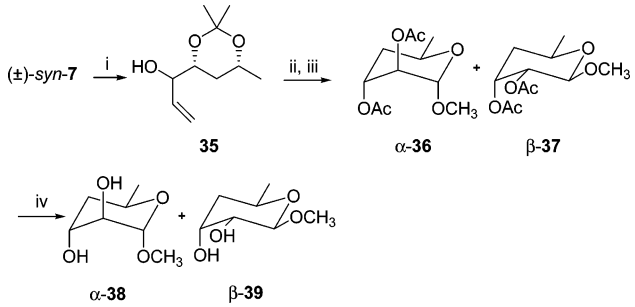
isolated from Norway spruce infested by *Trypodendron lineatum* Oliv.,[22] and (−)-tarchonanthuslactone,[23] a natural product isolated from a compositae, *Tarchonanthus trilobus*. In the first case it was prepared starting from (*R*)-methyl 3-hydroxybutanoate; in the second case chiral sulfoxides were employed to obtain enantioselectivity. Our chemoenzymatic approach afforded both enantiomers of *syn*-**33** in high ee and de.

Deprotection of (4*R*,6*R*)-**33** with acetic acid in aqueous tetrahydrofuran in the presence of a catalytic amount of concentrated HCl afforded 2,4,6-trideoxy-D-erithrohexopyranose (*R*,*R*-**34**). This kind of deoxy sugars can be prepared by aldol reactions catalyzed by 2-deoxyribose-5-phosphate aldolase (DERA).[24] (*R*,*R*)-**34**, in particular, was obtained by tandem aldol condensation of 3 mol of acetaldehyde catalyzed by DERA.

Our route to deoxy sugars through the key intermediate (*R*,*R*)-*syn*-**7** could be easily expanded. We also investigated the possibility of introducing a new stereogenic center bearing a hydroxylic group (Scheme 9).

We treated racemic *syn*-**7** with vinylmagnesium bromide in THF to obtain a mixture of the two possible diastereoisomers **35**. Ozonolysis combined with DMS quenching, followed first by treatment with methanol and catalytic $HCl_{(g)}$ and then with acetic anhydride in pyridine, afforded a mixture (two spots by TLC) of two pairs of acetylated methyl glycoside anomers. Column chromatography allowed us to isolate from the first eluted fractions a mixture of two acetylated methyl glycosides **36** and **37**. These latter derivatives were deacetylated with sodium methoxide in methanol to establish their configuration. Analysis of NMR spectra[25] allowed us to establish that the less

SCHEME 9[a]



[a] (i) Vinyl magnesium bromide in THF. (ii) O_3, CH_2Cl_2−MeOH, then DMS; MeOH, HCl Cat.; Ac_2O in pyridine. (iii) Column chromatography. (iv) MeONa cat. in MeOH.

polar fraction contained 4,6-dideoxy-α-D,L-arabinohexopiranoside and methyl 4,6-dideoxy-*β*-D,L-ribohexopiranoside. In the more polar fraction we could detect signals of 4,6-dideoxy-*β*-D,L-arabinohexopiranoside,[26] the NMR spectrum of which has not been reported.

D. Synthesis of the Carboxylic Fragment of Conagenin. We envisaged the possibility of employing *syn*,*syn*-**3** to obtain the carboxylic fragment of natural (+)-conagenin (**40**). (+)-Conagenin was originally isolated from fermentation broths of *Streptomyces roseosporus*.[27] It was found to stimulate activated T cells by producing lymphokines as a low molecular weight immunomodulator.[28] Improvement of the efficacy of antitumor agents, such as mitomycin C and adriamycin, by (+)-conagenin was also reported.[29] A few syntheses of (+)-conagenin have appeared in the literature.[30]

As we have previously shown, isolation of (2*R*,3*S*,4*S*)-*syn*,-*syn*-**3** was rather troublesome; thus, we focused our attention on a synthetic analogue of diol *syn*,*syn*-**3**, the furane-substituted diol **41**. It is well known that the furane ring can be cleaved by ozonolysis to give a carboxylic moiety (Scheme 10).

Aldol condensation of furfural with ethyl methyl ketone gave a 2:1 mixture of *anti*- and *syn*-**42** with high regioselectivity (>95%). The mixture of four stereoisomers of diol **41**, obtained upon $NaBH_4$ reduction, was treated with lipase PS in the usual conditions to afford a mixture of the four stereoisomers of monoacetate **43** and the unreacted diol **41**. The monoacetate

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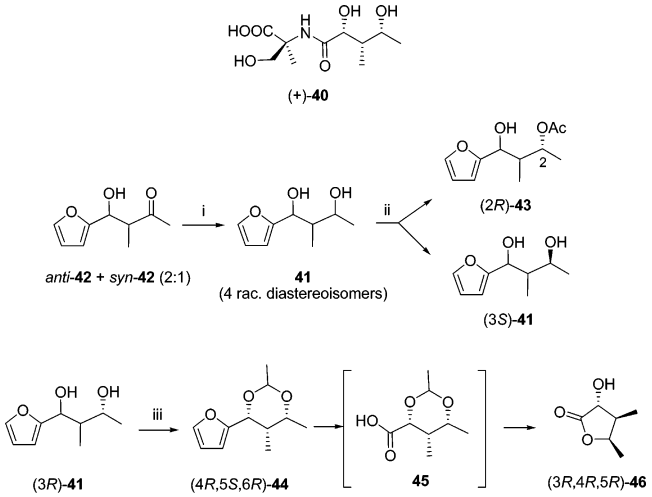
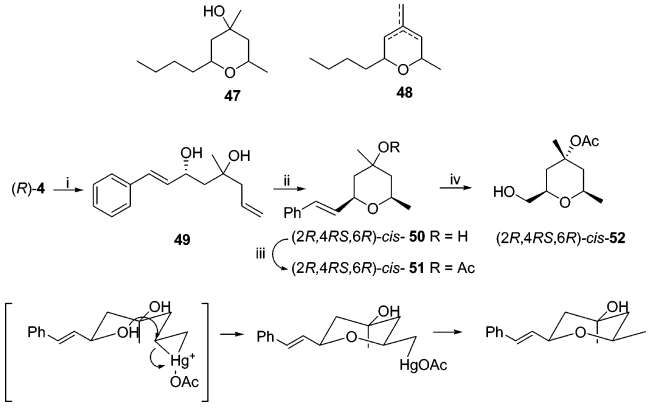
SCHEME 10[a]



[a] (i) $NaBH_4$, CH_2Cl_2/MeOH 2/1. (ii) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography. (iii) CH_3CHO, pyridium *p*-toluensulfonate. (iv) O_3, CH_2Cl_2/MeOH 2/1; $NaBH_4$. (v) NaOH 10%; HCl 10%.

SCHEME 11[a]



[a] (i) $CH{=}CHCH_2MgCl$, THF. (ii) $Hg(OAc)_2$, $NaBH_4$. (iii) AcONa, Ac_2O. (iv) O_3, then $NaBH_4$.

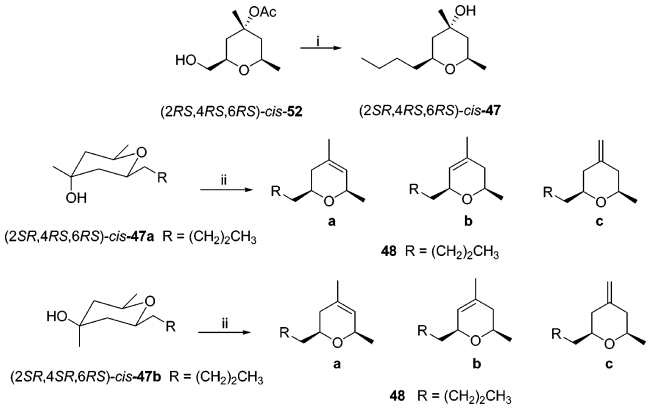
fraction was submitted to saponification and converted into the corresponding acetaldehyde acetal **44**. We found that column chromatography of the mixture of the four acetals allowed the isolation of (4*R*,5*S*,6*R*)-**44** as a pure compound. This latter was submitted to ozonolysis: the reaction mixture was treated with $NaBH_4$ and hydrolyzed with NaOH solution. We decided to not isolate the carboxylic acid **45** but to convert it into lactone (3*R*,4*R*,5*R*)-**46** by treatment with HCl 10% at room temperature for 1 h and extraction. The absolute stereochemistry of lactone **46**, precursor of the carboxylic moiety of conagenin, was known.[30e]

E. Synthesis of Substituted Tetrahydropyranes. We envisaged the possibility of employing hydroxy ketones **4**−**6** as precursors in the synthesis of substituted chiral tetrahydropyranes, as shown in Chart 1.

In particular, we were interested in the stereoisomers of compound **47**, potential precursors of Gyrane (**48**); so (*R*)-hydroxybutanone **4** was chosen as a model compound. Gyrane is a commercial fragrance showing *radiant green floral and spicy geranium notes*, which is formally a mixture of three regioisomers of two possible diastereoisomers (Scheme 11).

Addition of allylmagnesium chloride to hydroxy butanone (*R*)-**4** gave a 1:1 mixture of the two possible diastereoisomers

SCHEME 12[a]



[a] (i) TosCl, pyridine; $CH_3CH_2CH_2MgBr$, THF, Li_2CuCl_4. (ii) $POCl_3$, pyridine.

of adduct **49**, which was treated with $Hg(OAc)_2$ and $NaBH_4$ to give a 1:1 mixture of (2*R*,4*R*,6*R*)-*cis*-**50** and (2*R*,4*S*,6*R*)-*cis*-**50**, which could be separated by column chromatography. The ring closure was unexpectedly highly stereoselective, and only derivatives showing cis arrangement of the substituent at C_2 and C_6 were obtained. This high stereoselectivity can be attributed to formation of a cyclic mercurinium ion intermediate (Scheme 11), which undergoes ring opening by nucleophilic attack in a chairlike transition state. This hypothesis is in accordance with one of the mechanisms which have been postulated to describe the oxymercuration of olefins.[31] Diastereoisomers (2*R*,4*R*,6*R*)-*cis*-**50** and (2*R*,4*S*,6*R*)-*cis*-**50** were acetylated to give *cis*-(2*R*,4*R*,6*R*)-*cis*-**51** and (2*R*,4*S*,6*R*)-*cis*-**51**, respectively.

Ozonolysis of the latter acetylated compounds followed by $NaBH_4$ quenching afforded alcohols (2*R*,4*R*,6*R*)-*cis*-**52** and (2*R*,4*S*,6*R*)-*cis*-**52**.

From this step onward the synthetic sequence was to experiment on the two racemic diastereoisomers of alcohol *cis*-**52** (Scheme 12). We wished to investigate the course of the critical dehydration reaction (necessary to convert **47** into **48**) before starting the complete synthesis. The work devoted to preparation of all the enantiomerically pure isomers of Gyrane will be the subject of another publication.

Schlosser reaction performed on the two racemic diastereoisomers of compound *cis*-**52** afforded the two cis stereoisomers of **47**. Compounds *cis*-**47a** and *cis*-**47b** were dehydrated with $POCl_3$ in pyridine to afford, respectively, a 3:3:1 mixture of the three regioisomers **48a**, **48b**, and **48c** and a 1:1:3.5 mixture of **48a**, **48b**, and **48c**. The configuration of the carbon atom in position 4 was tentatively attributed on the basis of these considerations. $POCl_3$ dehydration is known to occur via a phosphoric ester which undergoes an anti elimination promoted by pyridine. When the OH group is axial, endo products are favored: their formation occurs via anti elimination of the axial hydrogens at C_3 and C_5. When the OH is equatorial, a hydrogen of the methyl group can meet the steric requirement for anti elimination so that the exo product is favored. The configuration of the C(4) in *cis*-**47a** and *cis*-**47b** was thus assigned on the basis of the outcome of the dehydration process.

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We submitted the two mixtures of Gyrane isomers to a preliminary evaluation (Givaudan perfumers) with the following results.

Mixture A (**48a**/**48b**/**48c** 3/3/1): Green, fruity, metallic vegetable note with the grapefruit−onion-like bitterness of Oxane and the herbal aspects of Buccoxime, stronger than mixture B both in top and dry down. Dry down linear, same just weaker but still stronger than Mixture B.

Mixture B (**48a**/**48b**/**48c** 1/1/3.5): Green, fruity, metallic vegetable note with the grapefruit−onion-like bitterness of Oxane and the herbal aspects of Buccoxime, very similar to mixture A but weaker in top and dry down. Dry down linear, green, metallic.

The preliminary results on odor evaluations are encouraging; the mixture enriched in the endo isomers seems to be more potent than that containing mainly the exo derivative. We plan to perform the synthesis of all single stereoisomers of Gyrane.

Conclusions

Lipase PS-mediated acetylation of 5-alken-2,4-diols **1**−**3** is a satisfactory approach to obtain these compounds in enantiomerically pure form. High stereochemical control on the configuration of the stereogenic centers can be achieved. The double bond can be cleaved by reaction with ozone to generate a useful carbonyl functionality and finally afford the enantiomerically pure chiral synthons **7**−**9**. The synthetic versatility of these derivatives has been shown by employing them as key intermediates in a new de novo approach to deoxy sugars. Combination of lipase-mediated acetylation and ozonolysis has been employed to obtain lactone **46**, precursor of the carboxylic moiety of conagenin.

Nucleophilic addition to the carbonyl group of hydroxy ketone **4**, followed by oxymercuration and double bond cleavage, represents a new path to chiral *cis*-tetrahydropyranes. Many chiral fragrances, not yet evaluated as single enantiomers, belong to this structural class, and this method can be easily extended to prepare them.

Experimental Section

(*S*,*E*)-4-Hydroxy-6-phenylhex-5-en-2-one ((*S*)-4) and (*R*,*E*)-5-Oxo-1-phenylhex-1-en-3-yl Acetate ((*R*)-14). Racemic **4** (60.0 g, 0.32 mol) was treated with lipase PS (20 g) in *tert*-butylmethyl ether solution (500 mL) in the presence of vinyl acetate (50 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give (*R*,*E*)-(+)-**14** (21.5 g, 29%) and (*S*,*E*)-(−)-**4** (27.3 g, 45%) (Enantiomeric ratio[32] E = 83).

Data of (*R*,*E*)-(+)-**14:** $[\alpha]_D = +67.5$ ($c = 1.18$, $CHCl_3$) [lit.[9] $[\alpha]_D = +65.3$ ($c = 0.52$, $CHCl_3$), ee >96%]; ^{1}H NMR[9] (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.64 (d, 1H, $J = 15.9$ Hz), 6.14 (dd, 1H, $J = 15.9$, 7.1 Hz), 5.81 (m, 1H), 2.95 (dd, 1H, $J = 16.4$, 7.6 Hz), 2.76 (dd, 1H, $J = 16.4$, 5.5 Hz), 2.19 (s, 3H), 2.06 (s, 3H); ^{13}C NMR[9] (62.90 MHz, $CDCl_3$) δ 204.4, 169.7, 135.9, 132.5, 128.4, 128.2, 126.6, 126.0, 70.3, 48.4, 30.4, 21.3. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.45; H, 6.87.

Data of (*S*,*E*)-(−)-**4**: $[\alpha]_D = -14.7$ ($c = 1.26$, $CHCl_3$) [lit.[9] $[\alpha]_D = -10.1$ ($c = 0.96$, $CHCl_3$), ee = 53%; lit.[33] $[\alpha]_D = +15.5$ ($c = 0.96$, $CHCl_3$), ee = 53% for (*R*)-**4**]; ^{1}H NMR[9] (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.64 (dd, 1H, $J = 15.9$, 1.1 Hz), 6.20 (dd, 1H, $J = 15.9$, 6.1 Hz), 4.76 (dq, 1H, $J = 1.2$, 6.1 Hz), 2.76 (d, 2H, $J = 6.1$ Hz), 2.22 (s, 3H); ^{13}C NMR[9] (62.90 MHz, $CDCl_3$) δ 208.7, 136.4, 130.3, 128.4, 127.7, 127.3, 126.4, 68.3, 49.4, 30.8. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.65; H, 7.53.

(2*R*,4*R*,5*E*)-6-Phenylhex-5-ene-2,4-diyl Diacetate ((2*R*,4*R*)-*syn*-11), (2*S*,4*R*,5*E*)-4-Hydroxy-6-phenylhex-5-en-2-yl Acetate ((2*S*,4*R*)-*anti*-13), and (3*R*,5*S*,1*E*)-5-Hydroxy-1-phenylhex-1-en-3-yl Acetate ((3*R*,5*S*)-*anti*-12). The 1:1 mixture of the two (2*RS*,4*R*)-**1** diastereoisomers (13.5 g, 0.070 mol) was treated with lipase PS (10 g) in *tert*-butylmethyl ether solution (250 mL) in the presence of vinyl acetate (25 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give, according to the elution order, (2*R*,4*R*)-*syn*-**11** (7.70 g, 40%), (2*S*,4*R*)-*anti*-**13** (0.98 g, 6%), and (3*R*,5*S*)-*anti*-**12** (5.10 g, 31%).

Data of (2*R*,4*R*)-*syn*-**11**: $[\alpha]_D = +68.5$ ($c = 1.62$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.70 (d, 1H, $J = 15.9$ Hz), 6.10 (dd, 1H, $J = 15.9$, 7.3 Hz), 5.48 (q, 1H, $J = 7.3$ Hz), 4.98 (m, 1H), 2.20−2.00 (m + 2s at 2.08 and 2.02, 7H), 1.85 (m, 1H), 1.28 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 170.4, 170.2, 136.2, 132.9, 128.6, 128.1, 126.9, 126.6; 71.8, 67.8, 40.6, 21.3, 20.2; GC/MS t_R 22.59 min, *m*/*z* 233 ($M^+ - 43$, 3), 216 (8), 174 (72), 156 (40), 145 (66), 131 (100). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.62; H, 7.21.

Data of (2*S*,4*R*)-*anti*-**13** containing 25% of (3*R*,5*S*)-*anti*-**12**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.65 (dd, 1H, $J = 15.9$, 1.0 Hz), 6.25 (dd, 1H, $J = 15.9$, 6.1 Hz), 5.23 (m, 1H), 4.32 (m, 1H), 2.11 (s, 3H), 1.85 (m, 2H), 1.34 (d, 3H, $J = 6.3$ Hz); GC/MS t_R 21.75 min, *m*/*z* 234 (M^+, 1), 191 (5), 174 (64), 131 (60), 115 (60), 104 (100). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.65; H, 7.58.

Data of (3*R*,5*S*)-*anti*-**12**: $[\alpha]_D = +99.0$ ($c = 2.27$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.63 (d, 1H, $J = 15.9$ Hz), 6.18 (dd, 1H, $J = 15.9$, 6.9 Hz), 5.67 (m, 1H), 3.81 (m, 1H), 2.13 (s, 3H), 1.78 (m, 2H), 1.23 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 171.4, 136.2, 132.2, 128.6, 128.1, 127.4, 126.6, 72.2, 63.7, 44.6, 23.2, 21.3; GC/MS t_R 21.46 min, *m*/*z* 234 (M^+, 3), 191 (62), 174 (65), 131 (100), 115 (60), 104 (60). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.84; H, 7.82.

(2*R*,4*R*,5*E*)-6-Phenylhex-5-ene-2,4-diol ((2*R*,4*R*)-*syn*-1). Saponification of (2*R*,4*R*)-*syn*-**11** (7.5 g, 0.027 mol) with KOH (2.34 g, 0.042 mol) in MeOH (150 mL) after the usual workup gave (2*R*,4*R*)-*syn*-**1** (4.41 g, 85%): mp 60−63 °C; $[\alpha]_D = +15.7$ ($c = 1.66$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.60 (d, 1H, $J = 15.9$ Hz), 6.20 (dd, 1H, $J = 15.9$, 6.5 Hz), 4.55 (q, 1H, $J = 6.5$ Hz), 4.11 (m, 1H), 1.71 (m, 2H), 1.23 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 136.7, 132.0, 130.0, 128.6, 127.9, 126.5, 73.4, 68.4, 45.1, 24.1; GC/MS t_R 20.59 min, *m*/*z* 192 (M^+, 14), 174 (19), 133 (48), 115 (48), 104 (100). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.27.

(2*S*,4*R*,5*E*)-6-Phenylhex-5-ene-2,4-diol ((2*S*,4*R*)-*anti*-1). Saponification of (3*R*,5*S*)-*anti*-**12** (5.0 g, 0.021 mol) with KOH (1.76 g, 0.031 mol) in MeOH (150 mL) after the usual workup gave (2*S*,4*R*)-*anti*-**1** (3.61 g, 88%): mp 50−52 °C, $[\alpha]_D = +40.5$ ($c = 1.13$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50−7.20 (m, 5H), 6.65 (dd, 1H, $J = 15.9$, 1.0 Hz), 6.30 (dd, 1H, $J = 15.9$, 5.9 Hz), 4.66 (qd, 1H, $J = 5.9$, 1.0 Hz), 4.21 (m, 1H), 1.81 (m, 2H), 1.27 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 136.8, 132.0, 130.0, 128.6, 127.6, 126.5, 70.4, 65.4, 44.4, 23.7; GC/MS t_R 20.56 min, *m*/*z* 192 (M^+, 10), 174 (20), 129 (50), 115 (50), 104 (100). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.06; H, 8.49.

(2*R*,4*R*,*E*)-5-Methyl-6-phenylhex-5-ene-2,4-diyl Diacetate ((2*R*,4*R*)-*syn*-15) and (2*S*,4*S*,*E*)-5-Methyl-6-phenylhex-5-ene-2,4-diol ((2*S*,4*S*)-*syn*-2). Racemic *syn*-**2** (21.0 g, 0.10 mol) was treated with lipase PS (20 g) in *tert*-butylmethyl ether solution (500 mL) in the presence of vinyl acetate (50 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on

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silica gel (hexane/ethyl acetate 9/1) to give diacetate (2*R*,4*R*)-*syn*-**15** (12.1 g, 41%) and diol (2*S*,4*S*)-*syn*-**2** (7.2 g, 35%) ($E = 1057$).

Data of (2*R*,4*R*)-*syn*-**15**: $[\alpha]_D = +7.5$ ($c = 0.94$, $CHCl_3$), ee > 99% (HPLC of the corresponding diol); ^{1}H NMR δ 7.40−7.10 (m, 5H), 6.49 (br s, 1H), 5.38 (t, $J = 6.5$ Hz, 1H), 4.94 (m,1H), 2.16−2.08 (m, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.90−1.80 (m, 1H), 1.84 (d, $J = 1.7$ Hz, 3H), 1.28 (d, $J = 6.5$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 170.5, 137.1, 135.3, 129.1, 128.4, 128.3, 126.9, 76.5, 68.2, 39.0, 21.4, 21.5, 20.3, 13.7; GC/MS t_R 23.77 min, *m*/*z* 247 ($M^+ - 43$, 7), 230 (15), 188 (43), 170 (67), 155 (100). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.55; H, 7.51.

Data of (2*S*,4*S*)-*syn*-**2**: $[\alpha]_D = +21.4$ ($c = 1.0$, $CHCl_3$), ee > 99% (HPLC); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35−7.00 (m,5H), 6.54 (br s, 1H), 4.41 (m, 1H), 4.09 (m, 1H), 1.89 (d, $J = 1.5$ Hz, 3H), (1.85−1.60, m, 2H), 1.20 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 142.3, 139.7, 131.1, 130.2, 128.6, 127.4, 80.7, 70.9, 45.4, 26.2, 15.8; GC/MS t_R 22.38 min, *m*/*z* 206 (M^+, 10), 188 (12), 147 (58), 129 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.80; H, 8.69.

Saponification of (2*R*,4*R*)-*syn*-**15** (11.90 g, 0.041 mol) with KOH (2.75 g, 0.049 mol) in MeOH (50 mL) gave (2*R*,4*R*)-*syn*-**2** (7.85 g, 93%): $[\alpha]_D = -20.8$ ($c = 0.94$, $CHCl_3$), ee > 99% (HPLC).

(2*R*,4*S*,*E*)-4-Hydroxy-5-methyl-6-phenylhex-5-en-2-yl Acetate ((2*R*,4*S*)-*anti*-16) and (3*R*,5*S*,*E*)-5-Hydroxy-2-methyl-1-phenylhex-1-en-3-yl Acetate ((3*R*,5*S*)-*anti*-17). Racemic *anti*-**2** (21.0 g, 0.10 mol) was treated with lipase PS (20 g) in *tert*-butylmethyl ether solution (500 mL) in the presence of vinyl acetate (50 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give monoacetate (2*R*,4*S*)-*anti*-**16** (8.43 g, 34%) and the other regioisomer (3*R*,5*S*)-*anti*-**17** (7.44 g, 30%).

Data of (2*R*,4*S*)-*anti*-**16**: $[\alpha]_D = +19.8$ ($c = 0.87$, $CHCl_3$); ^{1}H NMR δ 7.40−7.15 (m, 5H), 6.53 (br s, 1H), 5.16 (ddq, $J = 9.1$, 3.6, 6.2 Hz, 1H), 4.15 (dd, $J = 9.1$, 3.3, 1H), 2.05 (s, 3H), 1.91−1.83 (m, 1H), 1.87 (d, $J = 1.1$ Hz, 3H), 1.79 (ddd, $J = 14.3$, 9.1, 3.6, 1H), 1.30 (d, $J = 6.2$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 171.3, 139.7, 137.5, 128.9, 128.0, 126.4, 125.4, 73.9, 68.5, 42.1, 21.2, 20.6, 13.6; GC/MS t_R 23.34 min, *m*/*z* 248 (M^+, 2), 230 (5), 188 (50), 129 (100). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.39; H, 8.05.

Data of (3*R*,5*S*)-*anti*-**17**: $[\alpha]_D = +50.6$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR δ 7.35−7.15 (m, 5H), 6.55 (br s, 1H), 5.53 (dd, $J = 10.3$, 3.3 Hz, 1H), 3.79 (ddq, $J = 9.6$, 2.9, 6.2, 1H), 2.12 (s, 3H), 1.89 (d, $J = 1.1$ Hz, 3H), 1.90−1.80 (m, 1H), 1.74 (ddd, $J = 14.3$, 9.6, 3.3, 1H), 1.23 (d, $J = 6.2$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 171.3, 137.0, 136.1, 128.9, 128.1, 127.2, 126.7, 76.6, 63.8, 43.1, 23.2, 21.9, 14.0; GC/MS t_R 22.82 min, *m*/*z* 188 ($M^+ - 60.8$), 170 (23), 155 (50), 129 (100). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.71; H, 8.24.

(2*R*,4*S*,*E*)- and (2*S*,4*R*,*E*)-5-Methyl-6-phenylhex-5-ene-2,4-diol ((2*R*,4*S*,*E*)-*anti*-2 and (2*S*,4*R*,*E*)-*anti*-2). Saponification of (2*R*,4*S*)-*anti*-**16** (8.2 g, 0.033 mol) and (3*R*,5*S*)-*anti*-**17** (6.9 g, 0.029 mol) with KOH in methanol gave, respectively, (2*R*,4*S*,*E*)-*anti*-**2** (6.45 g, 95%, $[\alpha]_D = -32.8$ ($c = 0.86$, $CHCl_3$)) and (2*S*,4*R*,*E*)-*anti*-**2** (5.38 g, 94%, $[\alpha]_D = +30.6$ ($c = 0.96$, $CHCl_3$)): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.00 (m, 5H), 6.61 (br s, 1H), 4.47 (dd, $J = 7.3$, 3.8 Hz, 1H), 4.14 (m,1H), 1.86 (d, $J = 1.2$ Hz, 3H), 1.90−1.60 (m, 2H), 1.27 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 142.2, 139.7, 131.1, 130.2, 128.5, 126.7, 76.8, 67.6, 44.5, 25.7, 16.5; GC/MS t_R 22.33 min, *m*/*z* 206 (M^+, 9), 188 (12), 147 (60), 129 (100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.52; H, 8.95.

(2*R*,3*R*,4*S*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diyl Diacetate ((2*R*,3*R*,4*S*)-*anti*,*anti*-21) and (2*S*,3*S*,4*R*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diol ((2*S*,3*S*,4*R*)-*anti*,*anti*-3). Racemic *anti*,*anti*-**3** (10.0 g, 0.05 mol) was treated with lipase PS (10 g) in *tert*-butylmethyl ether solution (250 mL) in the presence of vinyl acetate (25 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give diacetate (2*R*,3*R*,4*S*)-*anti*,*anti*-**21** (5.35 g, 38%) and diol (2*S*,3*S*,4*R*)-*anti*,*anti*-**3** (3.50 g, 35%) ($E = 525$).

Data of (2*R*,3*R*,4*S*)-*anti*,*anti*-**21**: $[\alpha]_D = +51.7$ ($c = 1.31$, $CHCl_3$), ee = 98% (HPLC of the corresponding diol); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.57 (d, $J = 16.0$ Hz, 1H), 6.08 (dd, $J = 16.0$, 7.1 Hz, 1H), 5.43 (t, $J = 7.1$ Hz, 1H), 4.95 (quintuplet, $J = 6.3$ Hz, 1H), 2.17 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.19 (d, $J = 6.3$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) 169.9, 166.1, 135.9, 133.4, 128.2, 127.7, 126.3, 124.2, 74.9, 70.6, 40.8, 21.7, 20.9, 15.9, 10.3; GC/MS t_R 23.12 min, *m*/*z* 290 (M^+, 2), 230 (12), 188 (50), 133 (100). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.56; H, 7.49.

Data of (2*S*,3*S*,4*R*)-*anti*,*anti*-**3**: mp 71 °C, $[\alpha]_D = +16.5$ ($c = 1.31$, $CHCl_3$), ee > 99% (HPLC); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 6.58 (d, $J = 16.0$ Hz, 1H), 6.21 (dd, $J = 16.0$, 8.0 Hz, 1H), 4.23 (t, $J = 8.0$ Hz, 1H), 3.85 (dq, $J = 8.0$, 6.2 Hz, 1H), 1.68 (m, 1H), 1.24 (d, $J = 6.2$ Hz, 3H), 0.82 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 136.6, 131.9, 131.0, 128.5, 127.6, 126.5, 78.6, 72.6, 45.5, 21.6, 13.2. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.81; H, 8.77.

(2*R*,3*R*,4*R*,*E*)-4-Hydroxy-3-methyl-6-phenylhex-5-en-2-yl Acetate ((2*R*,3*R*,4*R*)-*anti*,*syn*-22) and (2*S*,3*R*,4*S*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diol ((2*S*,3*R*,4*S*)-*anti*,*syn*-3). Racemic *anti*,*syn*-**3** (10.0 g, 0.05 mol) was treated with lipase PS (10 g) in *tert*-butylmethyl ether solution (250 mL) in the presence of vinyl acetate (256 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give monoacetate (2*R*,3*R*,4*R*)-*anti*,*syn*-**22** (4.83 g, 39%) and diol (2*S*,3*R*,4*S*)-*anti*,*syn*-**3** (3.21 g, 32%) ($E = 164$).

Data of (2*R*,3*R*,4*R*)-*anti*,*syn*-**22**: mp 78°C, $[\alpha]_D = +44.2$ ($c = 0.92$, $CHCl_3$), ee = 95% (HPLC of the corresponding diol); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.20 (m, 5H), 6.59 (d, $J = 16.0$ Hz, 1H), 6.18 (dd, $J = 16.0$, 7.0 Hz, 1H), 5.37 (dq, $J = 2.4$, 6.5 Hz, 1H), 3.96 (t, $J = 7.0$ Hz, 1H), 2.05 (s, 3H), 1.72 (dquintuplet, $J = 2.4$, 7.0 Hz, 1H), 1.28 (d, $J = 6.5$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 171.6, 137.0, 132.2, 130.6, 128.7, 127.9, 126.7, 74.6, 70.5, 44.4, 21.4, 18.2, 10.1. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.31.

Data of (2*S*,3*R*,4*S*)-*anti*,*syn*-**3**: mp 75 °C, $[\alpha]_D = +7.36$ ($c = 0.92$, $CHCl_3$), ee = 97% (HPLC of the corresponding diol); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.60−7.20 (m, 5H), 6.63 (d, $J = 16.0$ Hz, 1H), 6.25 (dd, $J = 16.0$, 6.6 Hz, 1H), 4.32 (t, $J = 6.6$ Hz, 1H), 4.17 (dq, $J = 2.3$, 6.5 Hz, 1H), 1.78 (dquintuplet, $J = 2.3$, 6.6 Hz, 1H), 1.23 (d, $J = 6.5$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 136.7, 131.5, 131.1, 128.6, 127.6, 126.5, 76.5, 69.2, 43.4, 19.6, 11.5. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.82; H, 8.72.

Saponification of (2*R*,3*R*,4*R*)-*anti*,*syn*-**22** (4.50 g, 0.018 mol) with KOH (1.24 g, 0.022 mol) in MeOH (50 mL) gave (2*R*,3*S*,4*R*)-*anti*,*syn*-**3** (3.48 g, 94%): $[\alpha]_D = -6.98$ ($c = 0.92$, $CHCl_3$), ee = 95% (HPLC).

(3*S*,4*S*,*E*)-4-Methyl-5-oxo-1-phenylhex-1-en-3-yl Acetate ((3*S*,4*S*)-*anti*-24). A 2:1 mixture of *anti*-**6** and *syn*-**6** (5.1 g, 0.025 mol) was treated with lipase PS (2.0 g) in *tert*-butylmethyl ether solution (50 mL) in the presence of vinyl acetate (5 mL). After 7 days the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give, after crystallization form hexane, (3*S*,4*S*)-*anti*-**24** (1.48 g, 24%): mp 80 °C, $[\alpha]_D = +61.1$ ($c = 1.14$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.20 (m, 5H), 6.69 (d, 1H, $J = 16.0$ Hz), 6.03 (dd, 1H, $J = 16.0$, 7.6 Hz), 5.58 (t, 1H, $J = 7.6$ Hz), 2.93 (m, 1H), 2.21 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 208.9, 169.5, 135.8, 134.7, 128.4, 128.1, 126.5, 124.5, 75.6, 50.6, 28.8, 20.9, 12.7. GC/MS t_R 21.69 min, *m*/*z* 186 ($M^+ - 60$, 100), 171 (65), 128 (100). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.45; H, 7.49.

(2*S*,3*R*,4*S*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diol ((2*S*,3*R*,4*S*)-*anti*,*syn*-3) and (2*R*,3*R*,4*S*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diol ((2*R*,3*R*,4*S*)-*anti*,*anti*-3). Compound (3*S*,4*S*)-*anti*-**24** (1.30 g,

5.3 mmol) was treated with $NaBH_4$ (0.100 g, 2.7 mmol) in CH_2Cl_2/MeOH (2/1) (20 mL). After the usual workup the crude reduction mixture was treated with KOH (0.356 g, 6.4 mmol) in MeOH (20 mL). After the usual work up column chromatography (hexanes/ethyl acetate 8/2) afforded (2*S*,3*R*,4*S*)-(+)-*anti*,*syn*-**3** (ee > 99%, HPLC) (0.207 g, 19%) and (2*R*,3*R*,4*S*)-(−)-*anti*,*anti*-**3** (ee > 99%, HPLC) (0.262 g, 24%).

Preparation of Acetonides. Treatment of the suitable diol (0.022 mol) with dimethoxypropane (10 mL) and acetone (100 mL) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate gave, after the usual workup, the corresponding acetonide.

(a) (4*R*,6*R*,*E*)-2,2,4-Trimethyl-6-styryl-1,3-dioxane ((4*R*,6*R*)-*syn*-**25**). (2*R*,4*R*)-*syn*-**1** (4.30 g, 0.022 mol) gave (4*R*,6*R*)-*syn*-**25** (4.93 g, 95%): mp 53−55 °C; $[\alpha]_D = +41.4$ ($c = 1.51$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50−7.10 (m, 5H), 6.59 (d, 1H, $J =$ 15.9, 1.0 Hz), 6.17 (dd, 1H, $J = 15.9$, 6.2 Hz), 4.53 (ddd, 1H, $J =$ 2.5, 6.2, 11.4 Hz), 4.21 (ddq, 1H, $J = 2.5$, 11.4, 6.1 Hz), 1.62 (dt, 1H, $J = 13.0$, 2.6 Hz), 1.52 (s, 3H), 1.47 (s, 3H), 1.36 (m, 1H), 1.20 (d, 3H, $J = 6.1$ Hz);^{13}C NMR (62.90 MHz, $CDCl_3$) 136.8, 130.6, 130.1, 128.5, 127.6, 126.6, 98.8, 70.1, 65.0, 38.9, 30.4, 22.2, 19.9; GC/MS t_R 20.37 min, *m*/*z* 232 (M^+, 1), 174 (17), 157 (28), 104 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.41; H, 8.79.

(b) (4*S*,6*R*,*E*)-2,2,4-Trimethyl-6-styryl-1,3-dioxane ((4*S*,6*R*)-*anti*-**25**). Treatment of (2*S*,4*R*)-*anti*-**1** (3.50 g, 0.018 mol) gave (4*S*,6*R*)-*anti*-**25** (3.97 g, 94%) containing 10% of the starting diol: $[\alpha]_D =$ +71.2 ($c = 1.02$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.15 (m, 5H), 6.55 (d, 1H, $J = 16$ Hz), 6.22 (dd, 1H, $J =$ 16.0, 6.3 Hz), 4.52 (dt, $J =$ 8.8, 6.5 Hz, 1H), 4.06 (dquintuplet, 1H, $J =$ 8.8, 6.5 Hz), 1.90 (ddd, $J =$ 12.8, 8.8, 6.5 Hz, 2H), 1.73 (ddd, $J =$ 12.8, 8.8, 6.5 Hz, 2H), 1.42 (s, 6H), 1.23 (d, 1H, $J = 6.5$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 136.7, 131.9, 130.0, 128.6, 127.6, 126.5, 96.0, 69.5, 64.1, 42.2, 37.4, 22.2, 20.9; GC/MS t_R 19.98 min, *m*/*z* 232 (M^+, 1), 174 (12), 157 (14), 104 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.63; H, 8.53.

(c) (4*R*,6*R*,*E*)-2,2,4-Trimethyl-6-(1-phenylprop-1-en-2-yl)-1,3-dioxane ((4*R*,6*R*)-*syn*-**26**). Treatment of (2*R*,4*R*)-*syn*-**2** (7.60 g, 0.037 mol) gave (4*R*,6*R*)-syn-**26** (8.10 g, 89%): $[\alpha]_D = -10.6$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50−7.10 (m, 5H), 6.55 (br s, 1H), 4.37 (dd, 1H, $J =$ 11.1, 2.4 Hz), 4.07 (ddq, 1H, $J =$ 11.1, 2.4, 6.4 Hz), 1.87 (d, $J =$ 1.1 Hz, 3H), 1.62 (dt, 1H, $J =$ 13.0, 2.4 Hz), 1.53 (s, 3H), 1.47 (s, 3H), 1.41 (dt, $J =$ 13.0, 11.1 Hz, 1H), 1.21 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 138.4, 137.9, 129.2, 128.1, 126.5, 125.6, 98.9, 74.5, 65.3, 37.8, 30.5, 22.4, 20.1, 14.2; GC/MS t_R 21.58 min, *m*/*z* 246 (M^+, 5), 188 (36), 171 (30), 118 (100). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.14; H, 9.12.

(d) (4*R*,6*S*,*E*)-2,2,4-Trimethyl-6-(1-phenylprop-1-en-2-yl)-1,3-dioxane ((4*R*,6*S*)-*anti*-**26**). Treatment of (2*R*,4*S*)-*anti*-**2** (6.30 g, 0.030 mol) gave (4*R*,6*S*)-*anti*-**26** (6.77 g, 90%): $[\alpha]_D = -13.8$ ($c =$ 0.73, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.10 (m, 5H), 6.52 (br s, 1H, C*H*═C), 4.37 (dd, $J =$ 9.2, 6.5 Hz, 1H), 4.03 (dquintuplet, 1H, $J =$ 9.2, 6.5 Hz), 1.94 (ddd, $J =$ 13.0, 9.2, 6.5, 1H), 1.87 (d, $J =$ 1.1 Hz, 3H), 1.69 (ddd, $J =$ 13.0, 9.2, 6.5, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.24 (d, 1H, $J =$ 6.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 138.3, 138.0, 129.2, 128.2, 126.5, 125.1, 100.6, 71.7, 63.3, 38.7, 31.8, 25.3, 22.8, 14.3; GC/MS t_R 21.21 min, *m*/*z* 246 (M^+, 2), 188 (35), 118 (100). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.86; H, 8.78.

(e) (4*S*,5*S*,6*R*,*E*)-2,2,4,5-Tetramethyl-6-styryl-1,3-dioxane ((4*S*,5*S*,6*R*)-*anti*,*anti*-**27**). Treatment of (2*S*,3*S*,4*R*)-*anti*,*anti*-**3** (3.30 g, 0.016 mol) gave (4*S*,5*S*,6*R*)-*anti*,*anti*-**27** (3.58 g, 91%): $[\alpha]_D = -23.1$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50−7.10 (m, 5H), 6.59 (d, 1H, $J =$ 15.9 Hz), 6.11 (dd, 1H, $J =$ 15.9, 7.5 Hz), 4.06 (dd, 1H, $J =$ 10.0, 7.5 Hz), 3.68 (dq, 1H, $J =$ 10.0, 6.1 Hz), 1.52 (s, 3H), 1.45 (s, 3H), 1.34 (m, 1H), 1.21 (d, 3H, $J =$ 6.1 Hz), 0.81 (d, $J =$ 6.5 Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) 136.9, 133.3, 128.8, 128.6, 127.9, 126.8, 98.3, 76.9, 70.9, 41.0, 30.4, 20.1, 20.0, 12.8; GC/MS t_R 20.44 min, *m*/*z* 246 (M^+, 5), 188 (51), 171 (68), 104 (100). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.19; H, 9.15.

(f) (4*R*,5*S*,6*R*,*E*)-2,2,4,5-Tetramethyl-6-styryl-1,3-dioxane ((4*R*,5*S*,6*R*)-*anti*,*syn*-**27**). Treatment of (2*R*,3*S*,4*R*)-*anti*,*syn*-**3** (3.30 g, 0.016 mol) gave (4*R*,5*S*,6*R*)-*anti*,*syn*-**27** (3.66 g, 93%): $[\alpha]_D = -51.5$ ($c =$ 0.80, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.10 (m, 5H), 6.58 (d, 1H, $J =$ 16.1 Hz), 6.22 (dd, 1H, $J =$ 16.1, 7.2 Hz), 4.17 (quintuplet, 1H, $J =$ 6.5 Hz), 3.93 (t, *J* 7.5 Hz, 1H), 1.83 (m, 1H), 1.42 (s, 6H), 1.13 (d, $J =$ 6.5 Hz, 3H), 0.90 (d, 1H, $J =$ 6.8 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 136.7, 131.0, 128.9, 128.3, 127.4, 126.4, 100.4, 75.8, 64.8, 40.1, 24.9, 24.4, 16.6, 11.1; GC/MS t_R 20.32 min, *m*/*z* 246 (M^+, 1), 188 (35), 133 (100), 104 (73). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.81; H, 8.89.

Ozonolysis of Acetonides. A solution of the suitable acetonide (0.021 mol) in CH_2Cl_2−MeOH (2:1) (300 mL) was treated with ozone. The reaction mixture was quenched with triphenylphosphine and chromatographed on a silica gel column (hexane/ethyl acetate 8/2) to afford the corresponding carbonyl compound.

(a) (4*R*,6*R*)-2,2,6-Trimethyl-1,3-dioxane-4-carbaldehyde ((4*R*,6*R*)-*syn*-**7**). Acetonide (4*R*,6*R*)-*syn*-**25** (4.80 g, 0.021 mol) afforded (4*R*,6*R*)-*syn*-**7** (2.49 g, 75%); $[\alpha]_D = +72.5$ ($c = 1.18$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.30 (dd, 1H, $J =$ 12.2, 2.9 Hz), 4.05 (m, 1H), 1.74 (dt, 1H, $J =$ 12.8, 2.9 Hz), 1.48 (s, 6H), 1.30 (m), 1.22 (d, 1H, $J = 6.4$ Hz);^{13}C NMR (62.90 MHz, $CDCl_3$) 201.3, 99.1, 74.0, 64.5, 32.6, 29.8, 22.1, 19.5; GC/MS t_R 5.97 min, *m*/*z* 143 (M^+ − 15, 21), 129 (23), 59 (100), 43 (92). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.65; H, 8.86.

(b) Methyl 3,5-Dideoxy-L-threopentofuranoside) (L-**28**). Acetonide (4*S*,6*R*)-*anti*-**25** (3.80 g, 0.016 mol) afforded L-**28** as a 3:1 mixture of two anomers (0.802 g, 38%): ^{1}H NMR (250 MHz, $CDCl_3$) 4.85 (s, major anomer), 4.70 (d, $J =$ 4.5 Hz, minor anomer), 4.30−4.13 (m, both anomers), 3.53 (s, minor anomer), 3.38 (s, major anomer), 2.56−2.32 (m, both anomers), 1.49 (m, both anomers), 1.39 (d, $J =$ 6.1 Hz, major anomer), 1.34 (d, $J =$ 6.3 Hz, minor anomer); GC/MS t_R 4.38 min major anomer, *m*/*z* 101 (M^+ − 31, 9), 72 (48), 57 (100), 43 (42), t_R 5.27 min minor anomer, *m*/*z* 117 (M^+ − 15, 3), 101 (10), 72 (42), 57 (100), 43 (47). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.64; H, 9.27.

(c) 1-((4*R*,6*R*)-2,2,6-Trimethyl-1,3-dioxan-4-yl)ethanone ((4*R*,6*R*)-*syn*-**8**). Acetonide (4*R*,6*R*)-*syn*-**26** (7.80 g, 0.032 mol) afforded (4*R*,6*R*)-*syn*-**8** (3.76 g, 69%): $[\alpha]_D = +77.8$ ($c = 0.78$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 4.26 (dd, 1H, $J =$ 12.1, 2.6 Hz), 4.04 (ddq, 1H, $J =$ 11.6, 2.6, 6.4 Hz), 2.21 (s, 3H), 1.76 (dt, 1H, $J =$ 13.0, 2.6 Hz), 1.46 (s, 6H)), 1.27 (m, 1H), 1.20 (d, 3H, $J =$ 6.4 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 209.2, 99.0, 75.1, 65.0, 34.3, 30.2, 25.4, 22.2, 19.6; GC/MS t_R 8.88 min, *m*/*z* 157(M^+ − 15, 12), 129 (50), 59 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.61; H, 9.18.

(d) 1-((4*S*,6*R*)-2,2,6-Trimethyl-1,3-dioxan-4-yl)ethanone ((4*S*,6*R*)-*anti*-**8**). Acetonide (4*R*,6*S*)-*anti*-**26** (6.50 g, 0.026 mol) afforded (4*S*,6*R*)-*anti*-**8** (2.95 g, 65%): $[\alpha]_D = -61.8$ ($c = 1.10$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 4.23 (t, $J =$ 7.6 Hz, 1H), 3.96 (dquintuplet, 1H, $J =$ 9.9, 6.2 Hz), 2.22 (s, 3H), 2.01 (ddd, $J =$ 13.0, 7.6, 6.2, 1H), 1.71 (ddd, $J =$ 13.0, 9.9, 7.6, 1H), 1.40 (s, 6H), 1.21 (d, 1H, $J =$ 6.2 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 209.0, 100.6, 73.2, 62.8, 34.5, 26.2, 24.5, 21.8; GC/MS t_R 7.09 min, *m*/*z* 157 (M^+ − 15, 8), 129 (58), 59 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.96; H, 9.49.

(e) (4*S*,5*S*,6*S*)-2,2,5,6-Tetramethyl-1,3-dioxane-4-carbaldehyde ((4*S*,5*S*,6*S*)-*anti*,*anti*-**9**). Acetonide (4*S*,5*S*,6*R*)-*anti*,*anti*-**27** (3.30 g, 0.013 mol) afforded (4*S*,5*S*,6*S*)-*anti*,*anti*-**9** (1.54 g, 67%): $[\alpha]_D =$ −136.8 ($c = 0.70$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.51 (d, $J =$ 2 Hz), 3.82 (dd, 1H, $J =$ 11.0, 2 Hz), 3.66 (dq, 1H, $J =$ 10.0, 5.8 Hz), 1.53−1.39 (m + 2s, 7H), 1.21 (d, 3H, $J =$ 5.8 Hz), 0.88 (d, $J =$ 6.5 Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) 200.3, 98.4, 78.9, 70.3, 35.3, 29.9, 19.8, 19.7, 11.7; GC/MS t_R 8.24 min,

m/*z* 157 ($M^+ - 15$, 20), 143 (40), 59 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.63; H, 9.48.

(f) (4*S*,5*S*,6*R*)-2,2,5,6-Tetramethyl-1,3-dioxane-4-carbaldehyde ((4*S*,5*S*,6*R*)-*anti*,*syn*-**9**). Acetonide (4*R*,5*S*,6*R*)-*anti*,*syn*-**27** (3.40 g, 0.014 mol) afforded (4*S*,5*S*,6*R*)-*anti*,*syn*-**9** (1.52 g, 64%): $[\alpha]_D = -35.1$ (*c* = 0.90, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) 4.03 (quintuplet, 1H, *J* = 6.5, Hz), 3.80 (d, *J* = 6.5 Hz, 1H), 2.06 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.03 (d, 1H, *J* = 6.8 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 201.9, 100.8, 80.8, 64.8, 34.2, 29.8, 24.2, 17.2, 11.7; GC/MS t_R 6.52 min, *m*/*z* 172 (M^+, 0.5), 157 (7) 143 (23), 59 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.87; H, 9.52.

(4*R*,5*S*,6*R*)-4-(Furan-2-yl)-2,5,6-trimethyl-1,3-dioxane ((4*R*,5*S*,6*R*)-44). The mixture of diastereoisomeric diols (3*R*)-**41** (3.99 g, 0.023 mol), obtained by hydrolysis of acetates (2*R*)-**43** (6.0 g, 0.028 mol), was treated with acetaldehyde (3.10 g, 0.071 mol) in CH_2Cl_2 (25 mL) in the presence of pyridium *p*-toluenesulfonate (10 mg). The reaction mixture was concentrated under reduced pressure and chromatographed on a silica gel column to afford as the first eluted product acetal (4*R*,5*S*,6*R*)-**44** (0.460 g, 10%): $[\alpha]_D = -6.1$ (*c* = 0.80, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 (m, 1H), 6.38 (m, 1H), 6.27 (m, 1H), 4.95 (q, 1H, *J* = 5.1 Hz), 4.84 (br s, 1H), 4.15 (dq, *J* = 2.4, 6.5 Hz, 1H), 1.98 (m, 1H), 1.32 (d, *J* = 5.1 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.18 (d, 1H, *J* = 6.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 153.8, 142.2, 110.4, 108.3, 94.1, 75.6, 71.2, 33.6, 21.3, 18.8, 12.4; GC/MS t_R 13.02 min, *m*/*z* 196 (M^+, 10), 152 (15), 97 (100). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.48; H, 8.43.

(3*R*,4*R*,5*R*)-3-Hydroxy-4,5-dimethyl-dihydrofuran-2(3*H*)-one ((3*R*,4*R*,5*R*)-46). A solution of acetal (4*R*,5*S*,6*R*)-**44** (0.400 g, 2.04 mmol) in CH_2Cl_2−MeOH (2:1) (30 mL) was treated with ozone. The reaction mixture was quenched with $NaBH_4$ (0.077 g, 2.04 mmol) and then hydrolyzed with NaOH 10%. The water phase was acidified with HCl 10% and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane/ethyl acetate 8/2) to afford lactone (3*R*,4*R*,5*R*)-**46** (0.180 g, 68%): $[\alpha]_D = +57$ (*c* = 0.80, $CHCl_3$), p.o. = 95%, lit.[30e] $[\alpha]_D = +60$ (*c* = 0.80, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.71 (quintuplet, *J* = 6.8 Hz, 1H), 4.06 (d, *J* = 10.9 Hz, 1H), 2.56 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$); GC/MS t_R 7.32 min, *m*/*z* 112 ($M^+ - 18$, 2), 87 (8), 71 (100). Anal. Calcd for $C_6H_{10}O_3$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.54.

(4*R*,6*R*)-2,2,6-Trimethyl-1,3-dioxan-4-yl)methanol ((4*R*,6*R*)-*syn*-31). Reduction of (4*R*,6*R*)-**7** (2.35 g, 0.015%) with $NaBH_4$ (0.280 g, 7.0 mmol) in CH_2Cl_2−MeOH (2:1, 40 mL) at 0 °C afforded (4*R*,6*R*)-**31** (2.07 g, 87%): $[\alpha]_D = -13.3$ (*c* = 1.41, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.99 (m, 2H), 3.53 (m, 2H), 1.47 (s, 3H), 1.41 (s + m, 4H), 1.26 (m, 1H), 1.18 (d, 1H, *J* = 6.2 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 99.8, 69.8, 66.0, 64.7, 34.1, 30.1, 22.2, 19.9; GC/MS t_R 7.37 min, *m*/*z* 145 ($M^+ - 15$, 33), 129 (12), 59 (100), 43 (75). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.87; H, 10.18.

2-((4*S*,6*R*)-2,2,6-Trimethyl-1,3-dioxan-4-yl)acetonitrile ((4*R*,6*R*)-*syn*-32). Alcohol (4*R*,6*R*)-**31** (1.90 g, 0.012 mol) was treated with *p*-toluenesulfonyl chloride (3.42 g, 0.018 mol) in pyridine solution (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After the usual work up the crude reaction product was employed without any further purification. It was dissolved in DMSO (20 mL), and NaCN was added (0.882 g, 0.018 mol). The reaction was heated at 60 °C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and purified on a silica gel column (hexane/ethyl acetate 95/5) to afford (4*R*,6*R*)-**32** (1.25 g, 62%) containing 5% of the intermediate tosylate: $[\alpha]_D = +8.69$ (*c* = 1.22, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.25−3.85 (m, 2H), 2.51 (m, 2H, CH_2CN), 1.67 (dt, 1H, *J* = 12.9, 2.3 Hz), 1.46 (s, 3H), 1.41 (s, 3H), 1.31 (m, 1H), 1.20 (d, 1H); ^{13}C NMR (62.90 MHz, $CDCl_3$) 116.8, 99.2, 65.2, 64.6, 37.7, 29.9, 24.9, 21.9, 19.7; GC/MS t_R 10.26 min, *m*/*z* 154 ($M^+ - 15$, 31), 94 (46), 59 (54), 43 (100). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.75; H, 8.81; N, 8.14.

2-((4*R*,6*R*)-2,2,6-Trimethyl-1,3-dioxan-4-yl)acetaldehyde ((4*R*,6*R*)-*syn*-33). Nitrile (4*R*,6*R*)-**32** (1.10 g, 6.50 mmol) was reduced with DIBALH (1.2 M solution in toluene, 6.5 mL) in toluene (20 mL) at −10 °C. After the usual workup the crude reaction product was chromatographed on a silica gel column (hexane/ethyl acetate 8:2) to afford aldehyde (4*R*,6*R*)-*syn*-**33** (0.772 g, 69%): $[\alpha]_D = -10.5$ (*c* = 1.14, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.78 (t, 1H, *J* = 2 Hz), 4.38 (m, 1H), 4.00 (m, 1H), 2.51 (m, 2H, CH_2-CHO), 1.57 (dt, 1H, *J* = 12.7, 2.5 Hz), 1.40 (s, 3H), 1.38 (s, 3H), 1.17 (d + m, 4H, *J* = 6.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 200.1, 98.9, 64.8, 64.6, 49.5, 38.4, 30.1, 22.0, 19.7; GC/MS t_R 10.06 min, *m*/*z* 157 ($M^+ - 15$, 54), 97 (38), 69 (46), 59 (100), 43 (100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.65; H, 9.48.

(4*R*,6*R*)-6-Methyl-tetrahydro-2*H*-pyran-2,4-diol (or 2,4,6-Trideoxy-D-erithrohexopyranose) ((*R*,*R*)-34). Aldehyde (4*R*,6*R*)-*syn*-**33** (0.700 g, 4.10 mmol) was dissolved in THF (20 mL), and water was added till turbidity appeared. Acetic acid (1 mL) and one drop of HCl 37% were then added. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was neutralized and concentrated under reduced pressure to give (*R*,*R*)-**34** (0.276 g, 51%): ^{1}H NMR[24a] (250 MHz, $CDCl_3$) δ 5.32 (d, 1H, *J* = 4.8 Hz, α), 5.16 (br d, 1H, *J* = 10.0 Hz, *β*), 4.42 (ddq, 1H, *J* = 11.6, 2.2, 6.3 Hz, α), 4.32 (dq, 1H, *J* = 2.6, 5.4, *β*), 4.22 (m, 1H, α), 4.07 (ddq, 1H, *J* = 11.4, 6.3, 2.2 Hz, *β*), 1.40−2.00 (m, 4H, α + *β*), 1.23 (d, 3H, *J* = 6.3 Hz, *β*), 1.21 (d, 3H, *J* = 6.3 Hz, α); ^{13}C NMR (62.90 MHz, $CDCl_3$) α anomer δ 92.2, 65.0, 59.1, 39.7, 34.5, 21.4, *β* anomer δ 92.9, 66.5, 65.6, 39.6, 39.4, 21.3. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.64; H, 9.27.

Methyl 4,6-Dideoxy-α-D,L-arabinohexopiranoside (α-38) and Methyl 4,6-Dideoxy-*β*-D,L-ribohexopiranoside (*β*-39). The 1:1 mixture of (1*RS*)-**35** (1.50 g, 8.06 mmol) was treated with O_3 in CH_2Cl_2−MeOH solution (25 mL) at −78 °C. The reaction mixture was quenched with dimethyl sulfide. The solution was concentrated under reduced pressure. The residue was dissolved in methanol containing a catalytic amount of $HCl_{(g)}$. The mixture was concentrated and treated with acetic anhydride in pyridine. After the usual workup the residue (two spots by TLC, 0.987 g) was found to contain four acetylated methyl glycosides by GC/MS: 1st t_R 15.07 min (15%, GC/MS), 2nd t_R 15.61 min (32%, GC/MS), 3rd t_R 15.98 min (31%, GC/MS), 4th t_R 16.42 min (22%, GC/MS).

Column chromatography on a silica gel column (hexane/ethyl acetate 8/2) gave a first eluted fraction, which was a mixture of two acetylated methyl glycosides (0.235 g, 12%): α-**36** t_R 15.61 min (67%, GC/MS), *β*-**37** t_R 15.98 min (33%, GC/MS). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.74; H, 7.45.

Data of α-**36**:[25b] ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.91 (q, 1H, *J* = 3.0 Hz), 4.75 (m, 1H), 4.60 (br s, 1H), 4.01 (m, 1H), 3.38 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.90 −1.40 (m, 2H)), 1.22 (d, *J* = 6.3 Hz, 3H); GC/MS t_R 15.98 min, *m*/*z* ($M^+ - 60$, 2), 144 (32), 126 (37), 102 (57), 84 (50), 43 (100).

Data of *β*-**37**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.44 (q, 1H, *J* = 3.0 Hz), 4.70 (dd, 1H, *J* = 3, 8.1 Hz), 4.66 (d, 1H, *J* = 8.1 Hz), 4.14 (m, 1H), 3.50 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.90−1.40 (m, 2H), 1.25 (d, *J* = 6.3 Hz); GC/MS t_R 15.98 min, *m*/*z* ($M^+ - 60$, 2), 144 (33), 126 (30), 102 (67), 84 (67), 43 (100).

This mixture α-**36**−*β*-**37** was treated with a catalytic amount of sodium methoxide in methanol to give a 2:1 mixture of compounds α-**38** and *β*-**39**. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.95; H, 8.61.

Data of α-**38:** ^{1}H NMR[25f] (250 MHz, $CDCl_3$) δ 4.68 (br s, 1H), 4.11 (m, 1H), 3.87 (q, 1H, *J* = 3 Hz), 3.62 (m, 1H), 3.43 (s, 3H), 1.85−1.65 (m, 2H), 1.24 (d, *J* = 6.2 Hz); GC/MS t_R 10.02 min, *m*/*z* 131 ($M^+ - 31$, 4), 105 (5), 74 (12), 60 (100).

Data of β-**39**: ^{1}H NMR[25c] (250 MHz, $CDCl_3$) δ 4.51 (d, 1H, J = 8 Hz), 4.16 (q, 1H, J = 3 Hz), 4.01 (ddq, 1H, J = 11.5, 1.8, 6.1 Hz), 3.54 (s, 3H), 3.38 (dd, 1H, J = 3.2, 8 Hz), 1.88 (dt, J = 14.5, 2 Hz), 1.51 (ddd, J = 14.5, 3, 11.5 Hz), 1.23 (d, J = 6.3 Hz); GC/MS t_R 8.67 min, m/z 131 (M^+ − 31, 4), 105 (6), 74 (15), 60 (100).

Treatment of the mixture of four acetylated methyl glycosides with catalytic sodium methoxide gave a mixture of methyl glycosides in which we could detect the signals of β-**38**; not yet reported in the literature: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.68 (d, 1H, J = 1.7 Hz), 4.10 (q, 1H, J = 3.5 Hz), 4.00 (m, 1H), 3.54 (m, 1H), 3.53 (s, 3H), 2.00−1.40 (m, 2H), 1.26 (d, J = 6.1 Hz); GC/MS t_R 10.65 min, m/z (M^+ − 31, 3), 105 (5), 74 (10), 60 (100).

(2*R*,4*R*,6*R*,E)-2,4-Dimethyl-6-styryl-tetrahydro-2*H*-pyran-4-ol ((2*R*,4*R*,6*R*)-*cis*-50) and (2*R*,4*S*,6*R*,*E*)-2,4-Dimethyl-6-styryl-tetrahydro-2*H*-pyran-4-ol ((2*R*,4*S*,6*R*)-*cis*-50). (*R*)-**4** (15.0 g, 0.079 mol) was treated with allylmagnesium chloride (prepared from 0.174 mol of allyl chloride and 0.208 mol of Mg in THF solution) at −10 °C in THF solution (350 mL). The reaction mixture was quenched with NH_4Cl and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a 1:1 mixture of the two possible diastereoisomers of **49** (15.0 g, 82%), which was used for the subsequent step without further purification.

A solution of **49** (two stereoisomers, 15.0 g, 0.065 mol) was added to a mixture of mercuric acetate (20.7 g, 0.065 mol) in THF (100 mL) and water (25 mL). The reaction mixture was stirred overnight at room temperature. $NaBH_4$ (2.45 g, 0.065 mol) was added, and the mercury was allowed to settle. The reaction mixture was diluted with water and filtered on a Celite pad. The filtrate was extracted with ethyl acetate, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane:ethyl acetate 95/5) to give, in order of elution, (2*R*,4*R*,6*R*)-*cis*-**50** (4.82 g, 32%) and (2*R*,4*S*,6*R*)-*cis*-**50** (5.58 g, 37%).

Data of (2*R*,4*R*,6*R*)-*cis*-**50**: $[\alpha]_D$ = +8.63 (c = 0.90 $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43−7.15 (m, 5H), 6.61 (d, 1H, J = 15.9 Hz), 6.2 (dd, 1H, J = 15.9, 6.2 Hz), 4.40 (ddd, 1H, J = 11.5, 6.2, 2.2 Hz), 3.94 (ddq, 1H, J = 11.5, 2.2, 6.2 Hz), 1.68 (dt, 1H, J = 13.6, 2.2 Hz), 1.59 (dt, 1H, J = 13.6, 2.2 Hz), 1.48 (dd, 1H, J = 13.5, 11.6 Hz), 1.34 (dd, 1H, J = 13.5, 11.6 Hz), 1.29 (s, 3H), 1.24 (d, 3H, J = 6.3 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 137.0, 130.5, 130.4, 128.5, 127.5, 126.5, 73.6, 69.0, 68.6, 45.8, 44.2, 31.7, 21.7; GC/MS t_R 23.23 min, m/z 232 (M^+, 58), 214 (25), 199 (33), 148 (23), 131 (50), 104 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.64; H, 8.59.

Data of (2*R*,4*S*,6*R*)-*cis*-**50**: $[\alpha]_D$ = +14.3 (c = 0.95, $CHCl_3$);^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.15 (m, 5H), 6.60 (d, 1H, J = 15.9 Hz), 6.2 (dd, 1H, J = 15.9, 5.9 Hz), 4.04 (ddd, 1H, J = 11.0, 5.9, 2.0 Hz), 3.60 (m, 1H), 1.80−1.40 (m, 4H), 1.37 (s, 3H), 1.26 (d, 3H, J = 6.3 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 136.8, 130.7, 129.8, 128.5, 127.6, 126.5, 75.6, 71.2, 69.3, 47.8, 46.1, 26.90, 21.9; GC/MS t_R 23.40 min, m/z 232 (M^+, 24), 214 (27), 199 (24), 148 (38), 131 (45), 104 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.76.

(2*R*,4*R*,6*R*)-2,4-Dimethyl-6-((*E*)-styryl)-tetrahydro-2*H*-pyran-4-yl Acetate ((2*R*,4*R*,6*R*)-*cis*-51). A mixture of compound (2*R*,4*R*,6*R*)-*cis*-**51** (4.70 g, 0.020 mol) and sodium acetate (1.99 g, 0.024 mol) in acetic anhydride (25 mL) was refluxed for 2 h. The reaction mixture was poured into ice and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give compound (2*R*,4*R*,6*R*)-*cis*-**51** (4.93 g, 90%): $[\alpha]_D$ = −11.7 (c = 1.10, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.5−7.1 (m, 5H), 6.65 (d, 1H, J = 16.0 Hz), 6.19 (dd, 1H, J = 16.0, 6.0 Hz), 4.26 (ddd, 1H, J = 11.5, 6.0, 2.4 Hz), 3.79 (ddq, 1H, J = 11.5, 1.9, 6.2 Hz), 2.34 (m, 2H), 2.06 (s, 3H), 1.54 (s, 3H), 1.37 (dd, 1H, J = 13.8, 11.5 Hz), 1.24 (m + d, J = 6.3, 4H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 170.4, 136.8, 130.6, 129.7, 128.4, 127.6, 126.4, 79.7, 73.2., 68.6, 42.9, 41.7, 26.1, 22.4, 21.6; GC/MS t_R 24.24 min m/z 214 (M^+ − 60, 100), 199 (75), 131 (38). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.36; H, 7.97.

(2*R*,4*S*,6*R*)-2,4-Dimethyl-6-((*E*)-styryl)-tetrahydro-2*H*-pyran-4-yl Acetate ((2*R*,4*S*,6*R*)-*cis*-51). A mixture of compound (2*R*,4*S*,6*R*)-*cis*-**50** (5.40 g, 0.023 mol) and sodium acetate (2.30 g, 0.028 mol) in acetic anhydride (25 mL) was refluxed for 2 h. The reaction mixture was poured into ice and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give compound (2*R*,4*S*,6*R*)-*cis*-**51** (5.35 g, 85%): $[\alpha]_D$ = +8.48 (c = 0.78, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.15 (m, 5H), 6.61 (d, 1H, J = 16.0 Hz), 6.19 (dd, 1H, J = 16.0, 6.0 Hz), 4.09 (ddd, 1H, J = 11.5, 6.0, 2.4 Hz), 3.64 (ddq, 1H, J = 11.5, 2.1, 6.1 Hz), 2.26 (dt, 1H, J = 12.9, 2.1 Hz), 2.16 (dt, 1H, J = 12.9, 2.1 Hz), 1.99 (s, 3H), 1.71 (t, 1H, J = 12.3 Hz), 1.69 (s, 3H), 1.57 (t, 1H, J = 12.3 Hz), 1.26 (d, J = 6.2, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 170.3, 136.7, 130.8, 129.4, 128.4, 127.6, 126.4, 80.1, 74.7, 70.3, 44.5, 42.8, 22.4, 22.2, 21.8; GC/MS t_R 24.79 min, m/z 214 (M^+ − 60, 100), 199 (27), 131 (20). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.51; H, 8.14.

(2*R*,4*R*,6*R*)-2-(Hydroxymethyl)-4,6-dimethyl-tetrahydro-2*H*-pyran-4-yl Acetate ((2*R*,4*R*,6*R*)-*cis*-52). Compound (2*R*,4*R*,6*R*)-*cis*-**51** (4.80 g, 0.017 mol) was ozonized in methylene chloride/methanol 2:1 solution (70 mL) at −78 °C. The reaction mixture was quenched with sodium boron hydride. After column chromatography (hexane/ethyl acetate 8:2) compound (2*R*,4*R*,6*R*)-*cis*-**52** was recovered (2.40 g, 70%): $[\alpha]_D$ = −6.05 (c = 0.89, $CHCl_3$); ^{1}H NMR δ 3.71 (m, 2H), 3.63 (dd, 1H, J = 11.5, 3.0 Hz), 3.49 (dd, 1H, J = 11.5, 6.7 Hz), 2.27 (dt, 1H, J = 14.1, 2.2 Hz), 2.14 (dt, 1H, J = 14.1, 2.2 Hz), 2.01 (s, 3H), 1.52 (s, 3H), 1.27 (dd, 1H, J = 14.0, 11.5 Hz), 1.18 (d, J = 6.3, 3H), 1.16 (dd, 1H, J = 14.0, 11.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 170.3, 79.5, 73.1, 68.7, 65.8, 43.2, 37.1, 26.1, 22.3, 21.3; GC/MS t_R 14.58 min, m/z 171 (M^+ − 31, 1), 124 (5), 111 (100), 43 (55). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.47; H, 8.84.

(2*R*,4*S*,6*R*)-2-(Hydroxymethyl)-4,6-dimethyl-tetrahydro-2*H*-pyran-4-yl Acetate ((2*R*,4*S*,6*R*)-*cis*-52). (2*R*,4*S*,6*R*)-*cis*-**51** (5.20 g, 0.019 mol) was ozonized in methylene chloride/methanol 2:1 solution (70 mL) at −78 °C. The reaction mixture was quenched with sodium boron hydride. After column chromatography (hexane/ethyl acetate 8:2) compound (2*R*,4*S*,6*R*)-*cis*-**52** was recovered (2.61 g, 68%): $[\alpha]_D$ = −10.11 (c = 1.05, $CHCl_3$); ^{1}H NMR δ 3.67−3.47 (m, 4H), 2.13 (dt, 1H, J = 12.9, 2.1 Hz), 2.03 (dt, 1H, J = 12.9, 2.1 Hz), 1.97 (s, 3H), 1.63 (s, 3H), 1.58 (t, 1H, J = 12.3 Hz), 1.51 (t, 1H, J = 12.3 Hz), 1.21 (d, J = 6.3, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 170.2, 80.1, 74.6, 70.2, 66.0, 44.7, 38.5, 22.4, 22.2, 21.7; GC/MS t_R 15.78 min, m/z 171 (M^+ − 31, 2), 111 (100), 43 (55). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.30; H, 9.05.

(2*SR*,4*RS*,6*RS*)-2-Butyl-4,6-dimethyl-tetrahydro-2*H*-pyran-4-ol (*cis*-47a). Compound (2*RS*,4*RS*,6*RS*)-*cis*-**52** (2.30 g, 0.011 mol) was treated with *p*-toluenesulfonyl chloride (2.51 g, 0.013 mol) in pyridine. After the usual workup the tosylate derivative was dissolved in THF (50 mL), and Li_2CuCl_4[34] (1.3 mmol, prepared from 1.3 mmol of $CuCl_2$ and 2.6 mmol of LiCl) was added. Propylmagnesium bromide (prepared from 0.0132 mol of propyl bromide and 0.016 mol of magnesium) was added at −10 °C. The reaction mixture was stirred at 0 °C for 1 h and then poured into ice and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate; the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate 95/5) afforded *cis*-**47a** (1.31 g, 64%): ^{1}H NMR δ 3.77 (ddq, 1H, J = 11.5, 1.6, 6.2 Hz), 3.62 (m, 1H), 1.58−1.18 (m, 10H), 1.24 (s, 3H), 1.17 (d, J = 6.2, 3H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 72.9, 68.8, 68.7, 46.3, 44.3, 35.9, 31.72, 27.8, 22.8, 21.7, 14.0;

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GC/MS t_R 11.45 min, *m*/*z* 168 ($M^+ - 18$, 27), 153 (18), 129 (73), 87 (95), 58 (100), 43 (91). Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.85; H, 11.82.

(2*SR*,4*SR*,6*RS*)-2-Butyl-4,6-dimethyl-tetrahydro-2*H*-pyran-4-ol (*cis*-47b). Compound (2*RS*,4*SR*,6*RS*)-*cis*-**52** (2.50 g, 0.012 mol) was treated with *p*-toluenesulfonyl chloride (2.82 g, 0.015 mol) in pyridine (30 mL). After the usual workup the tosylate derivative was dissolved in THF. Propylmagnesium bromide (prepared from 0.0132 mol of propyl bromide and 0.016 mol of magnesium) was added at −10 °C. The reaction mixture was stirred and then poured into ice and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate; the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate 95/5) afforded *cis*-**47b** (1.36 g, 61%): ^{1}H NMR δ 3.45 (ddq, 1H, J = 11.5, 1.5, 6.1 Hz), 3.30 (m, 1H), 1.67−1.22 (m, 10H), 1.30 (s, 3H), 1.20 (d, J = 6.2, 3H), 0.90 (t, 3H, J = 6.8 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) 75.1, 70.9, 69.4, 48.2, 46.2, 36.1, 27.8, 26.1, 22.7, 21.9, 14.0; GC/MS t_R 11.82 min, *m*/*z* 168 ($M^+ - 18$, 6), 153 (3), 129 (71), 87 (94), 58 (88), 43 (100). Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.01; H, 11.98.

(2*RS*,6*SR*)-6-Butyl-2,4-dimethyl-3,6-dihydro-2*H*-pyran (48a or 48b), (2*SR*,6*RS*)-2-Butyl-4,6-dimethyl-3,6-dihydro-2*H*-pyran (48b or 48a), and (2*SR*,6*RS*)-2-Butyl-6-methyl-4-methylene-tetrahydro-2*H*-pyran (48c). (a) Dehydration of *cis*-**47a**. To a solution of *cis*-**47a** (1.20 g, 6.45 mmol) in pyridine (10 mL) at 0 °C phosphorus oxychloride (1.18 g, 7.74 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. After the usual workup the crude reaction product was chromatographed on a silica gel column (hexane/ethyl acetate 98/2) to afford a 3:3:1 mixture of the three regioisomers **48a**, **48b**, and **48c** (0.754 g, 58%).

(b) Dehydration of *cis*-**47b**. To a solution of *cis*-**47b** (1.20 g, 6.45 mmol) in pyridine (10 mL) at 0 °C phosphorus oxychloride (1.18 g, 7.74 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. After the usual workup the crude reaction product was chromatographed on a silica gel column (hexane/ethyl acetate 98/2) to afford a 1:1:3.5 mixture of the three regioisomers **48a**, **48b**, and **48c** (0.715 g, 55%). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.60; H, 11.89.

Data of **48a** and **48b**: ^{1}H NMR δ (main signals) 5.32 and 5.29 (m), 4.12 and 4.00 (m), 3.62 and 3.46 (m), 1.66 (s), 1.22 and 1.18 (d, J = 6.2 Hz), 0.90 (t, J = 6.8 Hz); GC/MS first peak t_R 8.65 min, *m*/*z* 153 ($M^+ - 15$, 8), 126 (29), 111 (100), second peak t_R 8.78 min, *m*/*z* 168 (M^+, 54), 153 (61), 110 (77), 43 (100).

Data of **48c**: ^{1}H NMR δ (main signals) 4.68 (t, 1H, J = 1.8 Hz), 3.37 (ddq, 1H, J = 11.2, 2.2, 6.1 Hz), 3.22 (m, 1H), 2.18 (m), 1.22 (d, 3H, J = 6.1 Hz), 0.90 (t, J = 6.8 Hz); GC/MS t_R 8.15 min, *m*/*z* 168 (M^+, 17), 124 (8), 111 (42), 67 (100).

Acknowledgment. The authors thank Dr. Philip Kraft (Givaudan Schweiz AG, Fragrance Research, Switzerland) for the odor descriptions. COFIN−Murst is acknowledged for financial support.

Supporting Information Available: Experimental details are given for the preparation of (*E*)-4-hydroxy-5-methyl-6-phenylhex-5-en-2-one (**5**), (3*RS*,4*RS*,5*E*)-4-hydroxy-3-methyl-6-phenylhex-5-en-2-one (*anti*-**6**), (3*RS*,4*SR*,5*E*)-4-hydroxy-3-methyl-6-phenylhex-5-en-2-one (*syn*-**6**), (3*RS*,4*RS*)-4-(furan-2-yl)-4-hydroxy-3-methylbutan-2-one (*syn*-**42**), and (3*RS*,4*SR*)-4-(furan-2-yl)-4-hydroxy-3-methylbutan-2-one (*anti*-**42**), reduction of hydroxy ketones **4**−**6** and **42** to diols **1**−**3** and **41**, configurational assignment of monoacetate (+)-*anti*-**17** by chemical correlation to (*R*)-(−)-**20**, lipase PS-mediated acetylation of **41** (four stereoisomers), preparation of (2*RS*,4*R*,5*E*)-6-phenylhex-5-ene-2,4-diol ((2*RS*,4*R*)-**3**) and (1*RS*)-1-((4*RS*,6*RS*)-2,2,6-trimethyl-1,3-dioxan-4-yl)prop-2-en-1-ol ((1*RS*)-*syn*-**35**), and X-ray analysis of *anti*,*anti*-**3**, *anti*,*syn*-**22**, and *anti*-**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060581W