8.72 (d, 4, J = 7 Hz, H-4'), 8.82 (s, 8, β-pyrrolic H), 9.09 (s, 4, H-2').

The porphyrin m-NO_2(TPP)H_2 (**11b**) (2.72 g, 3.42 mmol), 137 mL of concentrated aqueous HCl, and stannous chloride dihydrate (12.3 g, 54.8 mmol) were combined as previously reported.[29] The resulting mixture was made basic (140 mL of NH_4OH), and 50 mL of CH_2Cl_2 was added. After the suspension was thoroughly mixed, the resulting precipitate was collected by filtration. The dark solid collected was crushed to a powder and extracted with THF (4 × 150 mL). The resulting THF extract was filtered through a pad of silica gel. The filtrate was reduced to 30 mL, 50 mL of $CHCl_3$ was added, and the solution was again reduced to 30 mL when another 50 mL of $CHCl_3$ was added. After the solution was reduced to a final 20 mL, the precipitate was filtered and washed with $CHCl_3$ to give 2.00 g (87%) of m-NH_2-(TPP)H_2 (**11c**) as a fine purple microcrystals: R_f 0.46 (3:1 THF/hexanes); ^{1}H NMR (DMSO-d_6) δ −2.96 (s, 2, pyrrolic NH), 5.48 (br s, 8, NH_2), 7.01 (d, 4, J = 7 Hz, H-4'), 7.36-7.46 (m, 12, H-2', H-5', and H-6'), 8.92 (s, 8, β-pyrrolic H); FABMS m/z 675 (calcd for $C_{44}H_{34}N_8$ (M^+) 675).

5,10,15,20-Tetrakis[*m*-(*p*-tolylsulfonamido)phenyl]porphyrin (13) (*m*-(NHTs)(TPP)H_2). A mixture of m-NH_2(TPP)H_2 (**11a**) (100 mg, 0.148 mmol), p-toluenesulfonyl chloride (565 mg, 2.96 mmol), and triethylamine (0.52 mL, 3.7 mmol) in 30 mL of THF was stirred at room temperature for 72 h, then 10 mL of methanol was added, and the solution was stirred for an additional 14 h. The mixture was then diluted with ethyl acetate followed by the usual workup. The residue was dissolved in a minimal amount of CH_2Cl_2, and this solution was layered with benzene. The resulting red-purple crystals were collected by filtration and dried at 110 °C (0.2 mmHg) over P_2O_5 for 14 h to give 166 mg (87%) of m-(NHTs)(TPP)H_2 (**13**): R_f 0.62 (3:1 THF/hexanes); ^{1}H NMR (DMSO-d_6) δ −3.17 (s, 2, pyrrolic NH), 2.34 (s, 12, tosyl CH_3), 7.46 (d, 8, J = 7.5 Hz, tosyl m-H), 7.65 (br s, 4), 7.70-7.82 (m, 16), 7.87-7.96 (m, 4), 8.42-8.51 (m, 8, β-pyrrolic H), 10.55-10.62 (m, 4, tosyl NH); FABMS m/z 1290 (calcd for $C_{72}H_{58}N_8O_8S_4$ (M^+) 1290).

Tetrakis[*m*,*m*'-[methylene-(*p*-tolylsulfonyl)imino]]-*strati*-bis-(5,10,15,20-tetraphenylporphyrin) (14b) (*m*,*m*'-TsNCH$_2$-(TPP)H_2)$_2$). A mixture of m-(NHTs)(TPP) (**13**) (160 mg, 0.124 mmol), m-CH_2Br-(TPP)H_2 (**2**) (122 mg. 0.124 mmol), and Cs_2CO_3 (242 mg, 0.744 mmol) in 125 mL of DMF was stirred at room temperature for 14 h, then diluted with 50 mL of $CHCl_3$, and worked up in the usual manner. The residue obtained was dried further at 110 °C (0.05 mmHg) over P_2O_5 for 45 min. The residue (220 mg) was subjected to flash chromatography on silica, and elution with 100:1 $CHCl_3$/methanol provided 55 mg of a purple residue.

To simplify the preparative TLC,[24] the material thus obtained was metalated in the following manner.[37] To a refluxing $CHCl_3$ solution (8 mL) of this crude residue was added 5 mL of a methanolic solution containing 15 mg of potassium acetate (0.15 mmol) and 15 mg of Zn-$(OAc)_2$-$2H_2O$ (0.68 mmol). This mixture was refluxed for 30 min, and then the solvent was evaporated. The residue was dissolved in $CHCl_3$ and filtered over Celite. The filtrate was subjected to preparative TLC on a 0.5 × 200 × 200 mm silica plate eluting with 100:1 $CHCl_3$/methanol, and the second most nonpolar magenta band was isolated. This residue was dissolved in 0.3 mL of trifluoroacetic acid, and this solution was stirred for 15 min at room temperature, then diluted with $CHCl_3$, and washed with 5% aqueous NH_4OH solution followed by the standard workup to give 1.3 mg (1%) of m,m'-TsNCH$_2$-((TPP)H_2)$_2$ (**14**) as a purple solid: R_f 0.46 (100:1 $CHCl_3$/methanol); ^{1}H NMR δ −4.11, −4.07 (s, 2 each, pyrrolic NH), 2.25 (s, 12, tosyl CH_3), 5.19 (s, 8, CH_2), 6.95 (s, 4, H-2'''), 7.26 (d, 8, J = 8 Hz, tosyl m-H), 7.50 (d, 4, J = 8 Hz, H-4'''), 7.60 (t, 4, J = 8 Hz, H-5'''), 7.66 (d, 4, J = 8 Hz, H-4''), 7.76 (t, 4, J = 8 Hz, H-5''), 7.78 (s, 4, H-2''), 7.79 (d, 8, J = 8 Hz, tosyl o-H), 7.96 (d, 4, J = 8 Hz, H-6'''), 8.25 (br s, 8, β'-pyrrolic H), 8.35 (d, 4, J = 8 Hz, H-6''), 8.43 (s, 8, β-pyrrolic H); IR ν 3320 (w, N—H), 1600 (m, C=C) 1270, 1170, and 1100 (s, SO_2) cm^{-1}; UV/vis λ_{max} (ε × 10^{-3} cm^{-1} M^{-1}) 415 nm (314), 517 (16.6), 552 (7.71), 593 (5.69), 650 (4.03); FABMS m/z 1953 (calcd for $C_{120}H_{88}N_{12}O_8S_4$ (M^+) 1953).

Acknowledgment. We express our gratitude to Protos Corp. of Emeryville, CA, for a grant in support of this study.

Supplementary Material Available: ^{1}H NMR spectra of compounds **2**, **3b**, and **15** (X = $CF_3CO_2^-$, the aromatic region as compared to **3c**) each in $CDCl_3$ and **14** in $CDCl_3$ and CD_2Cl_2 (5 pages). Ordering information is given on any current masthead page.

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Highly Felkin-Anh Selective Hiyama Additions of Chiral Allylic Bromides to Aldehydes. Application to the First Synthesis of Nephromopsinic Acid and Its Enantiomer

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Contribution from the Institut für Organische Chemie der Freien Universität Berlin, Takustrasse 3, D-1000 Berlin 33, FRG, and Institut für Kristallographie der Freien Universität Berlin, Takustrasse 6, D-1000 Berlin 33, FRG. *Received October 15, 1990*

Abstract: The chromium(II)-mediated addition ("Hiyama reaction") of the chiral allylic bromides **13**, **15**, **19**, **22**, **24**, and **27** to achiral and chiral aldehydes proceeds with high Felkin-Anh selectivity with respect to the stereocenter at Cγ in the bromide (Table II). By double stereodifferentiation experiments (Tables III/IV) it was shown that the bromide is the stereodominating component in the addition. The methodology was applied to the first synthesis of nephromopsinic acid (−)-**69**, found in the lichen species *nephromopsis stracheyi*, and its enantiomer.

Allyl transfer reactions from reagents **1a-g** to aldehydes have acquired a central importance in natural product synthesis, due to their high regio- and stereochemical predictability.[1] The C-C connection regioselectively occurs at the γ-position of the double bond with concomitant allylic shift and migration of X to the aldehyde oxygen, from where it is removed by hydrolysis. The simple diastereoselection (syn or anti configuration at the newly

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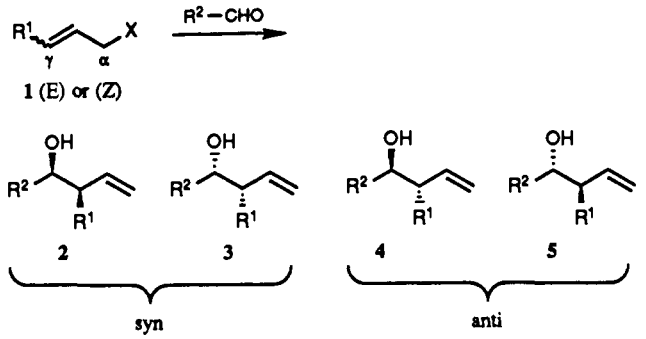
§ Preparative work.
⊥ Crystal structure analysis of compounds **44** and **57**.

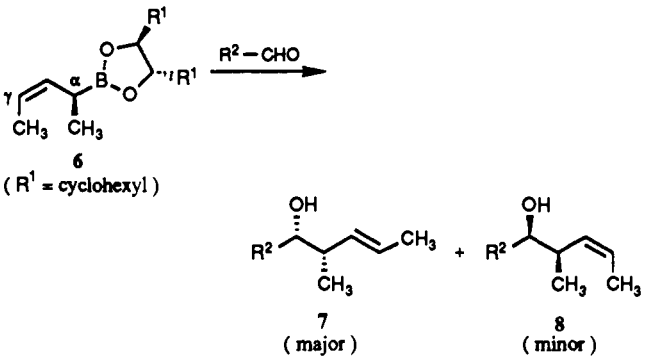
(1) (a) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (c) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932.

0002-7863/91/1513-4218$02.50/0



created stereocenters) can be controlled by an appropriate choice of X and the *E*/*Z* geometry of **1** (Table I).

With respect to enantioselectivity, high inductions have been achieved for **1a**/**b**[2] and **1c**/**d**[9] by chiral ligands at the boron atom, without changing the simple diastereoselection of the addition. A different approach has been developed by Hoffmann,[10] who employed α-chiral allylboronic esters **6**. The addition proceeds with efficient chirality transfer to the γ-position to furnish stereoisomers **7** and **8** in ratios of better than 90:10. The chiral substitution in the diol part of **6** has no effect on the enantioselectivity of the reaction. High enantiocontrol has been reported also for titanium reagents **1e**[11a-c] with appropriate chiral ligands R, for chiral allylic stannanes,[11d] and crotylmolybdenum complexes.[11e]



We studied the Hiyama reaction of the δ-chiral allylic bromides **9** with aldehydes. Presuming that the reaction continues to favor the anti diastereomers we had to expect **10** and **11** as the main products. The new questions to resolve then were as follows. (a) Which influence do chiral centers in **9** have on the ratio of **10**:**11**; especially, can the effect of the δ-center be modified by the introduction of additional stereocenters in the ε- and ζ-positions? (b) Which one of the established models developed for the interpretation of 1,2-induction in acyclic systems[12] may be used to interpret the stereochemical outcome? (c) How can the reaction be applied in natural product synthesis?

Table I. Selectivities for Allyl Transfer Reagents **1**

1	X	config	simple diastereoselection	ref
a	BR_2	*Z*	syn	2
b	BR_2	*E*	anti	2, 3
c	$B(OR)_2$	*Z*	syn	4
d	$B(OR)_2$	*E*	anti	4
e	$Ti(OR)_xR_y$	unknown	anti	5
f	SnR_3	*E* or *Z*	syn	6
g	$Cr^{II}R'_n$	unknown	anti	7, 8

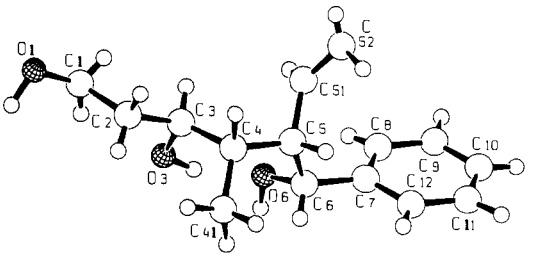
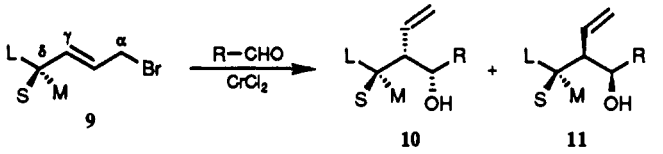


Figure 1. Crystal structure of **44**.



Synthesis of the Model Allylic Bromides (Scheme I). As shown in Scheme I, the following three types of Hiyama reagents were prepared: (a) those with one stereogenic center in the δ-position (**13** and **15**), (b) those with two stereogenic centers in the δ- and ε-position, both in syn-**19** and anti-**22** configurations, and (c) those with three stereogenic centers in the δ-, ε-, and ζ-positions, in *anti,anti*-**24** and *anti-syn*-**27** configurations. In all cases, the same standard sequence was employed, starting from the aldehydes (**12a**, **14a**, **18a**, **21a**, **23a**, and **26a**) which were converted into the (*E*)-acrylic esters (**12b**, **14b**, **18b**, **21b**, **23b**, and **26b**), reduced to the allylic alcohols (**12c**, **14c**, **18c**, **21c**, **23c**, **26c**), and then brominated with PBr_3. The aldehydes were partly known (**12a**,[13] **14a**[14]) or were prepared from known precursors (**16**,[15] **20**,[16] **25**[16]) as described in Scheme I.

Stereochemical Results

All Hiyama additions were performed in anhydrous THF at 0 to −5 °C over a period of 1−3 days in chemical yields between 55 and 90%. The chromium(II) chloride was prepared in situ from chromium(III) chloride and lithium aluminum hydride or purchased from Aldrich. The results were the same in both cases.

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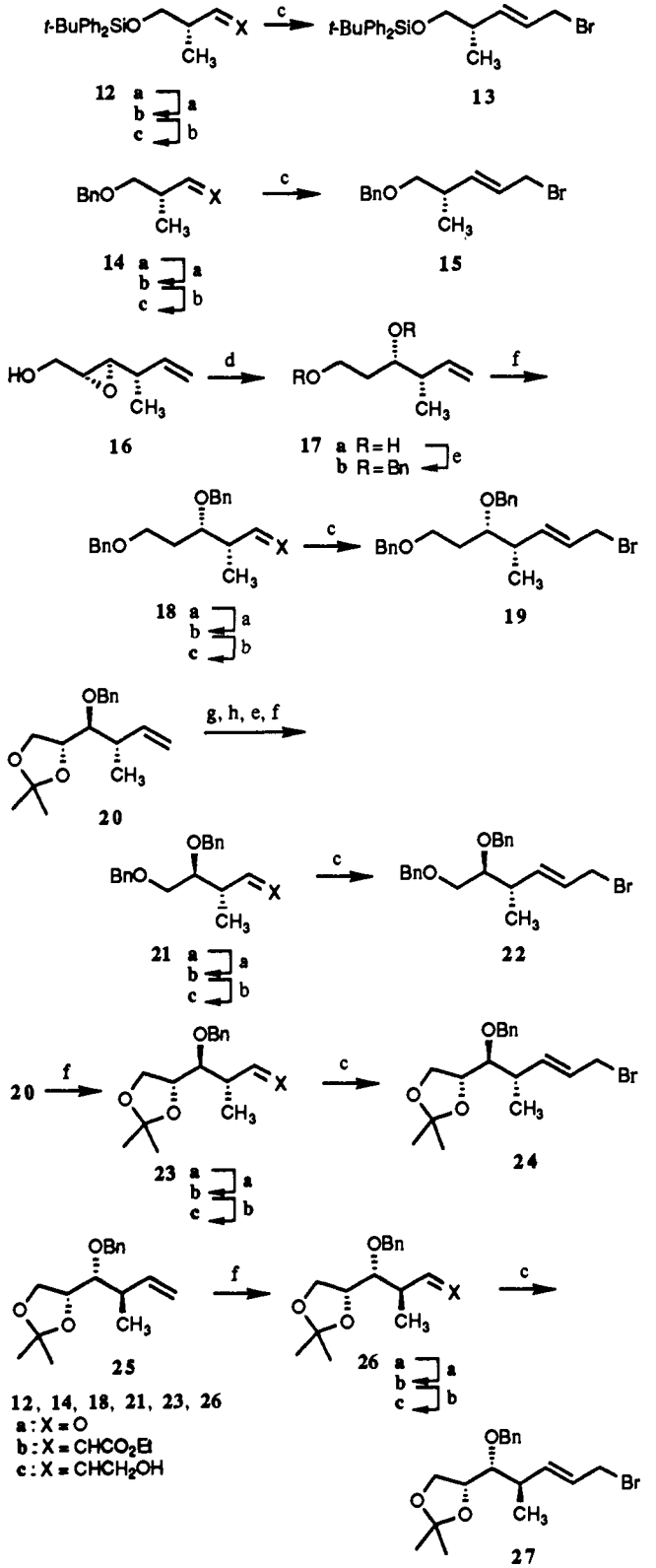
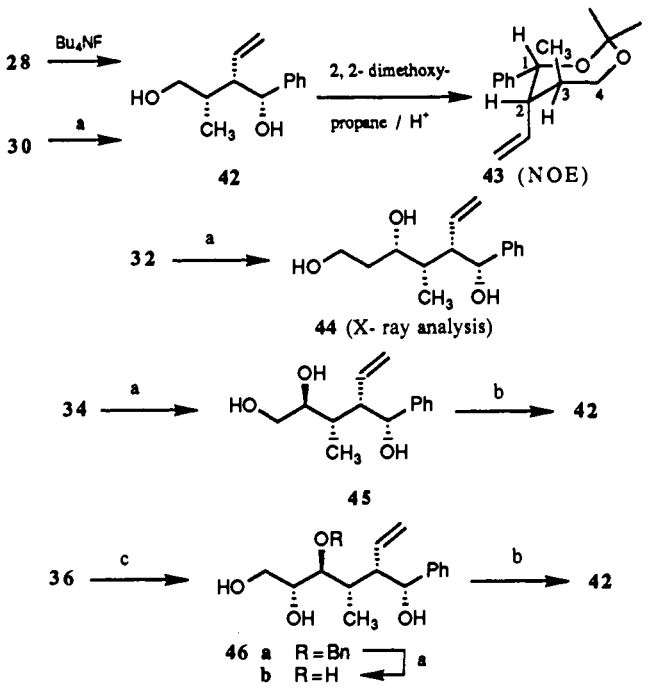
Scheme I[a]



[a] (a) $(EtO)_2POCH_2CO_2Et$/NaH, THF, 0–22 °C, 24 h, 70–95%; (b) DIBAH. toluene/Et_2O, −40 to −5 °C, 4 h, 78–91%; (c) PBr_3, Et_2O, −25 to 22 °C, 2 h, 79–98%; (d) Red-Al, toluene, 0–22 °C, 24 h, 85%: (e) BnCl/NaH, DMF, 0–22 °C, 24 h, 94–95%; (f) O_3 and then PPh_3, CH_2Cl_2, −78 to 22 °C, 84–85%; (g) *p*-TsOH, MeOH, 22 °C, 24 h, 82%; (h) H_5IO_6, THF, 22 °C, 20 min; and then 2 equiv of $LiAlH_4$, 0–22 °C, 24 h, 87%.

Achiral Aldehydes (Table II). Benzaldehyde and tetradecanal were chosen as achiral aldehydes. Bromides **13** and **15** reacted with benzaldehyde under moderate diastereofacial selectivity to furnish, almost independent of the O-protective group, diastereomers **28**/**29** and **30**/**31**, respectively, in ratios of 83:17 and 82:18, according to HPLC analysis. The bromides with two stereocenters (**19**/**22**) showed a significantly higher selectivity (>90:10) and furnished **32**/**33** and **34**/**35** as the only products. The presence of a third stereocenter (**24**/**27**) led to a further increase in selection; diastereomers **36**/**37**, **38**/**39**, and **40**/**41** were formed in a ratio of 96:4. On the $\Delta\Delta G^*$ scale each stereocenter accounts for 0.4–0.5 kcal/mol.

Scheme II[a]



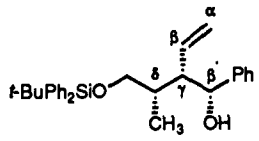
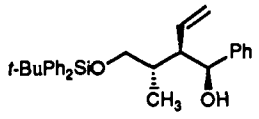
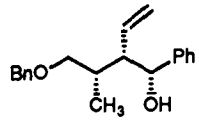
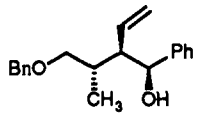
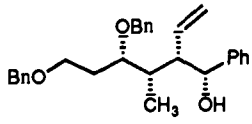
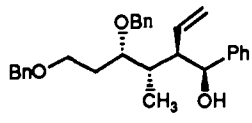
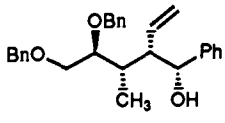
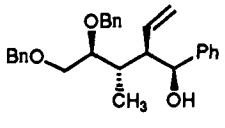
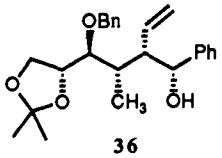
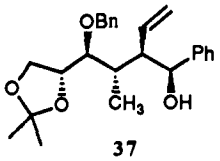
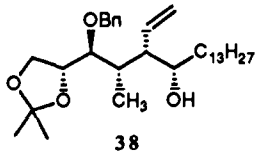
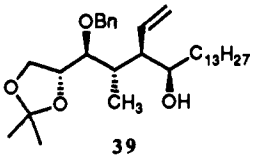
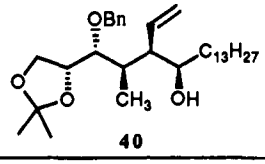
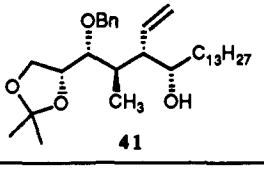
[a] (a) Na/NH_3, THF, −40 °C, 30 min, 74–91%; (b) H_5IO_6, THF, 22 °C, 20 min and then $LiAlH_4$, THF, 0–22 °C, 24 h, 95%; (c) *p*-TsOH, MeOH, 22 °C, 24 h, 94%.

The configuration at the newly created stereocenters of the major diastereomers were determined as shown in Scheme II. **28** and **30** were deprotected to afford the same diol **42**, which was converted into the acetonide **43** and analyzed by NOE difference spectroscopy. In particular, the strong interaction between 3-CH_3 and H-1 and 2 (11–14% NOE each) clearly indicated the configuration shown. **32** was debenzylated to give the crystalline triol **44**, which was submitted to a single-crystal X-ray analysis (Figure 1). Remarkably, an intramolecular hydrogen bond forming a seven-membered ring (HO–H distance 1.71 Å) can be recognized. **34** and **36** were degraded via **45** and **46**, respectively, to furnish diol **42**, identical in all respects (^1H and ^{13}C NMR, HPLC) with the material obtained from **28** and **30**. The structures of **38** and **40**, eventually, followed from the conversion of these adducts into [(−)- and (+)]-nephromopsinic acid (**69**) (vide infra). The configurations of the minor diastereomers were not rigorously established but assigned on the basis of the well-established simple diastereoselection of the Hiyama reaction.[8]

In conclusion, all major diastereomers have an all-syn arrangement of the β'-OH, γ-vinyl, and δ-methyl substituents. This means that (1) it is only the δ-center which determines the configuration at the newly created stereocenters (γ and β'), (2) the simple diastereoselection of the Hiyama reaction is not affected by the presence of chiral centers in the allylic bromide, and (3) additional stereocenters in the ϵ- and ζ-positions of the bromide increase the diastereofacial selectivity but have no influence on the sense of the asymmetric induction.

Stereochemical Interpretation (Scheme III). As the center at C-δ determines the sense of the asymmetric induction, the established models (**A**,[12a] **B**,[12b] and **C**[12c] in Scheme III) for acyclic 1,2-chirality transfer may be used. C-δ bears no heteroatom; consequently, the substituents in formulas **10**/**11** may be assigned according to their inert volumes (i.e., S = H, M = Me, L =

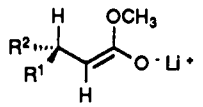
Table II. Hiyama Reaction of Achiral Aldehydes with Bromides **13**, **15**, **19**, **22**, **24**, and **27** (THF, 0 °C)

bromide	aldehyde	diasteromeric products	diastereomeric ratio	ΔΔG* (0°C), kcal/mol	combined yield, %
13	PhCHO	 **28**  **29**	**28 : 29** = 83 : 17	0.86	68
15	PhCHO	 **30**  **31**	**30 : 31** = 82 : 18	0.82	80
19	PhCHO	 **32**  **33**	**32 : 33** = 93 : 7	1.40	68
22	PhCHO	 **34**  **35**	**34 : 35** = 91 : 9	1.26	84
24	PhCHO	 **36**  **37**	**36 : 37** = 96 : 4	1.72	75
24	$H_{27}C_{13}CHO$	 **38**  **39**	**38 : 39** = 96 : 4	1.72	60
27	$H_{27}C_{13}CHO$	 **40**  **41**	**40 : 41** = 96 : 4	1.72	60

C-ϵ,ζ,η).[17] Additional stereocenters at C-ϵ,ζ apparently just increase the effective size of L. The major diastereomer is represented by formula **10** in all cases.

Models **A**–**C** are all based on the assumption of a Zimmerman–Traxler[18] chair geometry with an approximately antiperiplanar arrangement of L and the bulky CrR'_n moiety. Model **A** only is in accord with the observed preference for diastereomer **10**, so we have to discuss the advantages **A** may have over the alternatives **B** and **C**. It is easy to discard the allylic 1,3-strain model **C**, because in our allylic bromides there is no cis substituent at Cβ, in contrast to the otherwise related ester enolates **47**,[19] which in fact do add electrophiles according to model **C**. Why is model **B** inferior to **A**? The main reason may be the angle ϑ formed by the trajectory and the olefinic plane. According to the Zimmerman–Traxler model ϑ should be obtuse which is more in accord with model **A** (normal angle ϑ of ca. 110°) than with model **B**, for which angles ϑ of $\leq 90°$ have been postulated. On comparing the steric crowding in both models, **A** is good with respect to "outside crowding" (R← →S) and bad with respect to "inside

(17) Winterfeldt, E. *Prinzipien und Methoden der Stereoselektiven Synthese*; F. Vieweg & Sohn: Verlagsgesellschaft/Braunschweig, 1988; p 1.
(18) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(19) (a) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. (b) Bernhard. W.; Fleming, I.: Waterson. D. *J. Chem. Soc., Chem. Commun.* **1984**, 28.



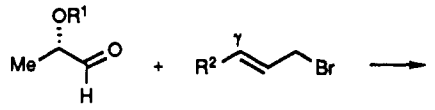
47

crowding" (M syn to two "ring" bonds). The reverse is true of **B**. Inspection of molecular models reveals that in fact substituent R comes very close to S (in **A**) and M (in **B**), respectively. Thus, the stereocontrolling factor in the addition obviously is to avoid outside crowding. Finally, Felkin–Anh boat conformations (**D**) also may be excluded: **D** would suffer from severe R/R′ interactions and cannot compete with the chair (**A**).

In conclusion, the Hiyama addition of our chiral allylic bromides can stereochemically be described in terms of the Felkin–Anh model. Previously we have shown that the same model may also be applied in the addition of achiral allylic bromides to α-chiral aldehydes **48**.[20] Thus, both components of the Hiyama reaction obey the same stereocontrolling principle! This result is somewhat surprising as the Felkin–Anh model normally is considered as characteristic of electron-deficient reaction sites.

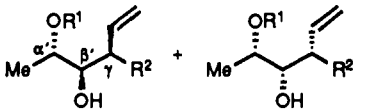
Obviously, it is not the positive or negative polarization of the reaction site which decides on Felkin–Anh vs Houk transition states but the relative importance of "inside" and "outside" crowding and, hence, the angle ϑ of the trajectory. ϑ, in turn, is determined by the overall geometry of the transition state and varies significantly with the individual reaction types.[12b]

Double Stereodifferentiation (Tables III and IV). As mentioned above, α-chiral aldehydes like (*S*)- and (*R*)-**48** react with achiral allylic bromides like **49** under Felkin–Anh control to yield the *anti*-diol diastereomers **50** preferentially. The ratio of **50**:**51** varies between 89:11 and >99:1, depending on the nature of R^2 and the



(S) - 48 49

a R^1 = THP R^2 = Me, Et,
b R^1 = TBDMS *n*-Bu, Ph



50 51

O-protective group R^1. The highest selectivity was achieved for R^1 = *t*-$BuMe_2Si$ and R^2 = *n*-C_4H_9. Consequently, efficient double stereodifferentiation should be expected in additions of our chiral allylic bromides (e.g., **13**, **19**, **24**, and **27**) to aldehyde **48**. As **48** is available in form of both enantiomers, we were sure that both the matched and the mismatched situation[21] could be realized. From the stereoselectivities observed in either case, it should be possible to determine which component has the stronger stereodirecting influence.

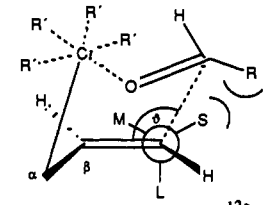
The matched combinations are shown in Table III. For instance, adduct **52** has an all-syn arrangement of substituents at the centers Cδ, Cγ, and Cβ′. It is obvious that the configuration at Cβ′ also fits into the α′,β′-*anti*-diol geometry demanded by the aldehyde.

The consonant stereochemical effects from both partners led to the exclusive (>97%) formation of the adducts **52**–**54** in reasonable chemical yields (55–72%). The configurational assignments are based on the experiments shown in Scheme IV. Thus, **52b** was converted into the acetonide **55**, in which the diol moiety is incorporated into a conformationally defined dioxolane ring. NOE experiments clearly show the cis location of H-4 and -5.

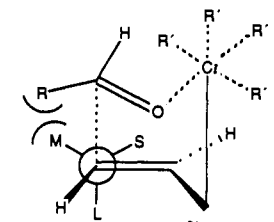
(20) Mulzer, J.; Schulze, T.; Strecker, A.; Denzer, W. *J. Org. Chem.* **1988**, *53*, 4098.

(21) Horeau, A.; Kagan, H. B.; Vigneron, J. P. *Bull. Soc. Chim. Fr.* **1968**, 3795. Review: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

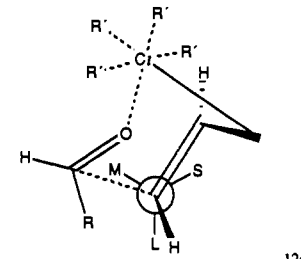
Scheme III. Transition State Models



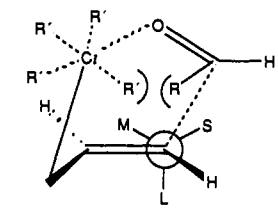
A (Felkin-Anh-Model)[12a] → 10



B (Houk-Model)[12b] → 11

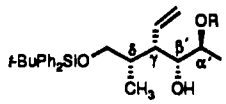
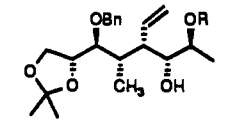
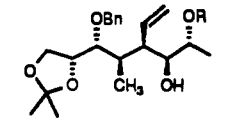


C (Allylic 1,3-Strain-Model)[12c] → 11



D (Boat-Felkin-Anh-Model) R′ = Cl, Br, THF → 10

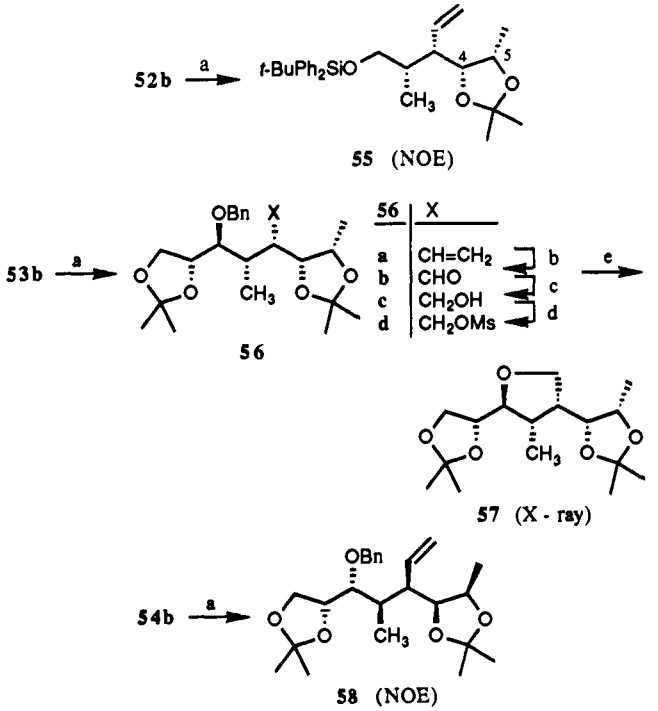
Table III. Double Stereodifferentiation: Matched Combinations

bromide	aldehyde	major diasteromeric product		yield, %
13	(S) - 48a	 52	a R = THP, b R = H	62
24	(S) - 48b	 53	a R = TBDMS, b R = H	72
27	(R) - 48b	 54	a R = TBDMS, b R = H	55

53b was transformed into carbinol **56c** via **56a**–**b**. The mesylate **56d** was unstable and cyclized to the tetrahydrofuran derivative **57** which was submitted to a single-crystal X-ray analysis (Figure 2). The spontaneous formation of **57** is surprising, as the central tetrahydrofuran ring has to accommodate two pseudo-axial substituents at C-4 and C-5, respectively. **54b**, like **52b**, was converted into the acetonide **58** and analyzed by NOE difference spectroscopy.

The mismatched combinations are the subject of Table IV. For instance, the addition of bromide **24** to aldehyde (*R*)-**59** exclusively

Scheme IV[a]



[a] (a) *p*-TsOH catalyst, $Me_2C(OMe)_2$, CH_2Cl_2; 22 °C, 24 h, 84–98%; (b) O_3 and then PPh_3, CH_2Cl_2, −78 to 22 °C, 85%; (c) $LiAlH_4$, Et_2O, 0–22 °C, 3 h, 95%; (d) CH_3SO_2Cl/NEt_3, CH_2Cl_2, 0–22 °C, 24 h, 71%, (e) *p*-TsOH, MeOH and then $Me_2C(OMe)_2$, CH_2Cl_2, 22 °C, 75%.

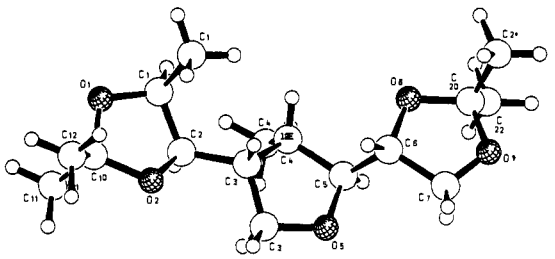
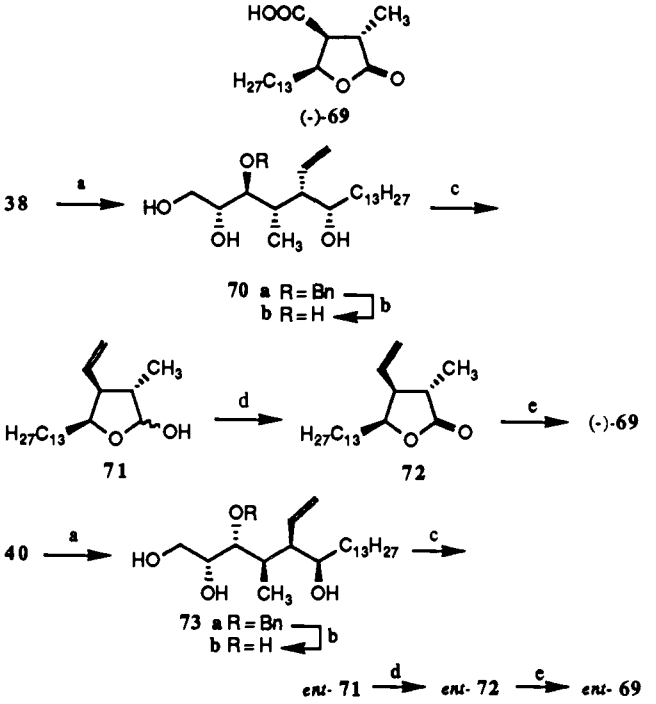


Figure 2. Crystal structure of **57**.

gave compound **60**, with an all-syn arrangement at the stereocenters C-4–C-7. This means that the stereochemical course of the reaction has been dominated by the bromide, to which the aldehyde has succumbed. Similarly, bromide **27** reacts with (*S*)-**59** to **62** with the same predominance of the bromide over the aldehyde. The configurations of **60** and **62** were proven by converting them into the natural product dihydrocanadensolide ((−)-**61**) and its enantiomer.[22]

Analogous results were obtained from the addition of **27** to (*S*)-**48b**, which led to the all-syn products **63a,b**. The configuration of the C-6,7-diol moiety in **63a** was established by NOE experiments with the corresponding acetonide **64**. So far, allylic bromides with three contiguous stereocenters have been employed. Remarkably, bromide **19**, with two stereocenters, reacted with (*R*)-**48b** to give **65** with the same high diastereoselectivity. In contrast, bromide **13**, with only one stereocenter, gave a mixture of three diastereomers with aldehyde (*R*)-**48a**. Obviously, not only the Felkin–Anh induction of the bromide but also the simple diastereoselection of the Hiyama addition itself have broken down! Finally, to test an extreme case, aldehyde **67a** was tried. **67b** had been shown to exhibit a very high (>95%) anti-Felkin–Anh selectivity toward crotyl(II) chromium.[23] This should lead to a mismatched combination of **67a** with bromide **27**. In fact, adduct **68** was obtained as a 2.5:1 mixture of diastereomers in low

Scheme V.[a] Synthesis of Nephromopsinic Acid and Its Enantiomer



[a] (a) *p*-TsOH catalyst, MeOH, 22 °C, 24 h, 84/85%; (b) Na/NH_3, THF, −40 °C, 30 min, 92/94%; (c) H_5IO_6, Et_2O, 22 °C, 1 h and then K_2CO_3, MeOH, 15 min, 73%; (d) 5 equiv of PCC, CH_2Cl_2, 0–22 °C, 2 h, 92%; (e) $RuCl_3$ catalyst/$NaIO_4$, $CCl_4/H_2O/CH_3CN$, 22 °C, 2 h, 62%.

chemical yield (ca. 40%). Sideproducts, resulting from the reduction and self-coupling of **27**, were isolated in appreciable amounts. These results clearly mark the limits of the stereodominance of the allylic bromide: reliable stereocontrol in the sense of an all-syn arrangement at Cδ, Cγ, and Cβ′ can only be expected for bromides with more than one chiral center and stereochemically "weak" aldehydes like **48** or **59**. Of course it remains to be clarified which structural elements in an aldehyde decide on its stereochemical "strength" or "weakness".

Synthesis of Nephromopsinic Acid (69) (Scheme V). Nephromopsinic acid ((−)-**69**) was isolated from the lichen species *nephromopsis stracheyi* by Asano and Azumi in 1935;[24] its structure was assigned by van Tamelen and Huneck much later.[25] As **69** has never been synthesized and its structure was only assigned on the basis of plausibility arguments, we chose this target molecule as a test case for our newly developed Hiyama methodology. To demonstrate the flexibility of the approach we prepared both enantiomers of **69**. The synthesis of (−)-**69** (Scheme V) starts with adduct **38**, which was deprotected to give tetrol **70b**. Degradation with periodic acid furnished lactol **71** and lactone **72** after oxidation with PCC. RuO_4 oxidation of the double bond delivered (−)-**69**, identical in every respect with an authentic sample of the natural product. Similarly, adduct **40** was converted into (+)-**69** via **73a,b**.

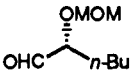
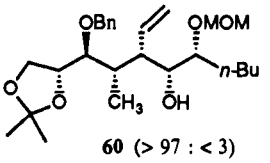
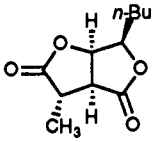
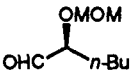
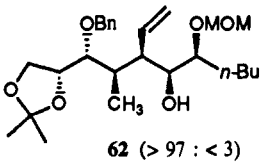
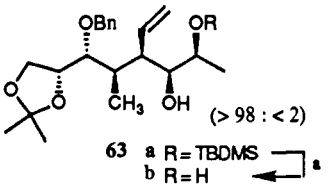
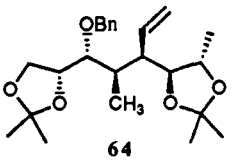
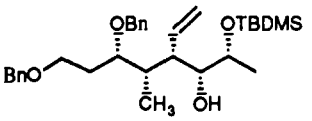
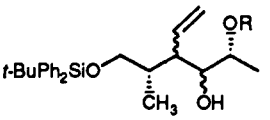
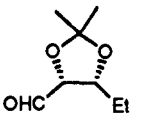
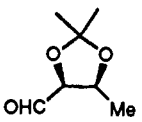
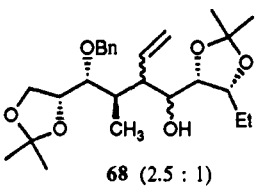
Epilogue. In conclusion, the addition of chiral allylic bromides to aldehydes under Hiyama conditions proceeds with high and reliable stereocontrol, the bromide acting as the stereodominant component. As both the aldehyde and the allylic bromide can easily be prepared from simple precursors, the reaction provides a rapid access to relatively complex adducts. Further studies of scope and limitation as well as applications to natural product synthesis are underway in our laboratory.

Experimental Section

General Methods. NMR spectra were recorded on either a Bruker AM 270 SY or AC 250 instrument (^1H: 270/250 MHz, internal TMS;

(22) Mulzer, J.; Kaltner, L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 679.
(23) Fronza, G.; Fuganti, C.: Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Chem. Lett.* **1984**, 335.
(24) Asano, M.; Azumi, T. *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 995.
(25) van Tamelen, E. E.; Rosenberg Bach, S. *J. Am. Chem. Soc.* **1958**, *80*, 3079. Huneck. S.; Follmann, G. *Z. Naturforsch.* **1967**, *22*, 666.

Table IV. Double Stereodifferentiation: Mismatched Combinations

bromide	aldehyde	major diasteromeric product (ratio)	yield, %	derivative
24	 (R) - **59**	 **60** (> 97 : < 3)	63	 (-) - **61**
27	 (S) - **59**	 **62** (> 97 : < 3)	65	(+) - **61**
27	(S) - **48b**	 **63** a R = TBDMS, b R = H (> 98 : < 2)	66	 **64**
19	(R) - **48b**	 **65** (> 98 : < 2)	90	
13	(R) - **48a**	 **66** a R = THP, b R = H (3 : 1 : 1)	80	
27	 **67a**  **67b**	 **68** (2.5 : 1)	40	

^{13}C: 68/63 MHz, internal $CDCl_3$). IR spectra were recorded on a Perkin-Elmer 580 B infrared spectrophotometer. Mass spectra were measured at 80 eV on a Varian MAT 711 mass spectrometer. Optical rotations were obtained in $CHCl_3$ with a Perkin-Elmer Model 241 polarimeter. HPLC separations were performed on Nucleosil 50 with particle sizes of 5 μm (analytical) and 7 μm (preparative), with UV and RI detection. Preparative column chromatography was performed on silica gel Merck 60, 0.040–0.063 mm. All reactions were carried out in purified solvents under an argon atmosphere and were monitored on TLC plates (Merck 5554).

Starting Materials. *O*-Tetrahydropyranyl- and *O*-((*tert*-butyldimethyl)silyl)lacetaldehydes **48a/b** were prepared from the corresponding O-protected lactates[26] ((*S*)-series, ethyl ester; (*R*)-series, isobutyl ester). Aldehyde **67a**, derived from D-(+)-ribono-1,4-lactone, was prepared as described in the literature for similar compounds.[27] (*R*)-2,3-*O*-isopropylideneglyceraldehyde was prepared from D-mannitol. Tetradecanal was purchased from Fluka AG. (*R*)- and (*S*)-MOM-2-hydroxyhexanal **59** can be synthesized from (*R*)- and (*S*)-benzylglycidol (Aldrich) via a Cu(I)-mediated epoxide opening with PrMgBr in the primary position and conversion into the aldehydes by routine operations. (*S*)-*O*-benzylglycidol could be prepared from D-mannitol according to a procedure described by Takano.[28]

Hiyama Reaction. General Procedure. In a typical experiment, $CrCl_3$ (4.28 g, 27 mmol) was suspended in THF (100 mL). $LiAlH_4$ (0.51 g, 13.5 mmol) was added in small portions under vigorous stirring at 0 °C. After the evolution of hydrogen had ceased, the mixture was stirred at 22 °C for 30 min. The aldehyde (15 mmol) and the allylic bromide (10 mmol), both dissolved in THF (20 mL), were added at 0 to −5 °C. After stirring the mixture for 36 h at this temperature, saturated aqueous sodium hydroxide (15 mL) and anhydrous Na_2SO_4 (20 g) were added. The mixture was stirred for 20 min at 22 °C and filtered over a pad of Celite/Na_2SO_4 (7:1). The filtrate was concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate mixtures (3:1 to 10:1)) to give the Hiyama adducts in 55–90% yield. The Hiyama adducts **28/29**, **38/39**, and **68** were separated by HPLC. Diastereomeric ratios were determined by ^1H NMR and HPLC analysis or by weighing the diastereomers after separation.

Synthesis of Allylic Bromide 13 from 12a. Ethyl (4S)-5-(((*tert*-Butyldiphenyl)silyl)oxy)-4-methyl-2(*E*)-pentenoate (12b). NaH (0.36 g, 15.0 mmol) was suspended in THF (100 mL), and triethyl phosphono-

(26) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.

(27) Jäger, V.; Häfele, B. *Synthesis* **1987**, 801.

(28) Takano, S.; Akiyama. M.; Ogasawara. K. *Synthesis* **1985**, 503.

acetate (3.63 g, 16.2 mmol) in THF (50 mL) was added dropwise at 0 °C. After stirring for 2 h at room temperature, aldehyde **12a** (4.05 g, 12.3 mmol) in THF (50 mL) was added at 0 °C. After stirring for an additional 24 h at room temperature, the mixture was treated with H_2O (20 mL). THF was removed by evaporation under reduced pressure, and the residue was extracted with diethyl ether. Drying of the combined organic layers ($MgSO_4$) and evaporation of volatiles furnished the crude ester, which was purified by column chromatography (hexane/ethyl acetate (3:1). **12b** (4.65 g, 95%) was obtained as a colorless oil: $[\alpha]^{20}_D$ −9.7 (*c* 1.5, $CHCl_3$); IR (film) ν_{max} 3070, 2960, 2930, 2900, 2860, 1720, 1650, 1470, 1460, 1425, 1390, 1365, 1305, 1270, 1240, 1180, 1150, 1110, 1035, 1010, 1000, 985, 825, 805, 740, 700, 690, 615, 505 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 9 H, *t*-$BuCH_3$), 1.07 (d, 3 H, CH_3), 1.28 (t, 3 H, *J* = 7 Hz, ester-CH_3), 2.54 (m, 1 H, H-4), 3.58 (d, 2 H, H-5), 4.19 (q, 2 H, *J* = 7 Hz, ester-CH_2), 5.81 (dd, 1 H, *J* = 15.5, 1 Hz, H-2), 6.95 (dd, 1 H, *J* = 15.5, 7 Hz, H-3), 7.36 (m, 6 H, aryl-H), 7.62 (m, 4 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.25, 15.57, 19.26, 26.58, 26.83, 39.08, 60.11, 67.59, 121.10, 127.64, 129.64, 133.61, 135.59, 151.24, 166.63; MS (EI 40 °C) *m/e* 340 (22.78), 339 (81.16), 227 (100), 199 (94.91), 183 (44.96). Anal. Calcd for $C_{24}H_{32}O_3Si$: C, 72.68; H, 8.13. Found: C, 72.40; H, 8.18.

(2*S*)-1-*O*-((*tert*-Butyldiphenyl)silyl)-2-methyl-3(*E*)-pentene-1,5-diol (12c). To a stirred solution of acrylic ester **12b** (4.50 g, 11.35 mmol) in diethyl ether (100 mL), was added DIBAH (3.6 g, 17 mL, 25 mmol, 2.2 equiv as a 1.5 M solution in toluene) dropwise at −40 °C. After stirring for 4 h at −5 °C, water (2 mL, 111 mmol, 10 equiv) and Na_2SO_4 (16 g, 113 mmol, 10 equiv) were added, and the mixture was allowed to warm up to room temperature. After complete crystallization of the resulted precipitate, the mixture was filtered. Evaporation of volatiles and column chromatography (hexane/ethyl acetate (3:1)) provided **12c** (3.21 g, 80%): colorless oil; $[\alpha]^{20}_D$ −2.8 (*c* 2.3, $CHCl_3$); IR (film) ν_{max} 3350, 3070, 3050, 2960, 2930, 2900, 2860, 2740, 1470, 1390, 1360, 1190, 1110, 1005, 970, 825, 740, 700, 615, 505 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.04 (d, 3 H, *J* = 7.5 Hz, CH_3), 1.06 (s, 9 H, *t*-$BuCH_3$), 1.35 (s, 1 H, OH), 2.40 (m, 1 H, H-2), 3.49 (dd, 1 H, *J* = 10, 6 Hz, H-1), 3.53 (dd, 1 H, *J* = 10, 7 Hz, H-1), 4.05 (mc, 2 H, H-5), 5.67 (mc, 2 H, H-3, H-4), 7.39 (mc, 6 H, aryl-H), 7.65 (mc, 4 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 16.44, 19.34, 26.91, 38.94, 63.84, 68.57, 127.59, 128.82, 129.56, 134.00, 135.50, 135.64; MS (EI, 40 °C) *m/e* 199 (100), 57 (91.28), 41 (89.9). Anal. Calcd for $C_{22}H_{30}O_2Si$: C, 74.53; H, 8.53. Found: C, 74.33; H, 8.63.

(2*S*)-5-Bromo-1-*O*-((*tert*-butyldiphenyl)silyl)-2-methyl-3(*E*)-penten-1-ol (13). Allylic alcohol **12c** (7.50 g, 21.15 mmol) in diethyl ether (400 mL) was treated dropwise under vigorous stirring with phosphorous tribromide (2.25 g, 8.31 mmol, 0.39 equiv) in ether (50 mL) at −25 °C. After stirring for an additional 2 h at 22 °C, the solution was poured into a concentrated aqueous $NaHCO_3$ solution (200 mL) at 0 °C. The organic layer was separated, and the aqueous phase was extracted with ether (3 times with 100 mL each). The combined etheric phases were dried ($MgSO_4$), and, after evaporation of volatiles, the chromatographed residue (hexane/ethyl acetate (3:1)) gave **13** (8.63 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ +1.1 (*c* 1.1, $CHCl_3$); IR (film) ν_{max} 3070, 3050, 2960, 2930, 2900, 2860, 1470, 1425, 1390, 1360, 1205, 1110, 1090, 1030, 1010, 700, 615, 505, 490 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (d, 3 H, *J* = 7.5 Hz, CH_3), 1.04 (s, 9 H, *t*-$BuCH_3$), 2.40 (m, 1 H, H-2), 3.51 (d, 2 H, *J* = 7 Hz, H-5), 3.91 (t, 2 H, H-1), 5.68 (mc, 2 H, H-3, H-4), 7.36 (m, 6 H, aryl-H), 7.62 (m, 4 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 16.14, 19.30, 26.89, 33.31, 38.86, 68.25, 126.12, 127.61, 129.58, 133.85, 135.62, 138.84; MS (EI, 80 °C) *m/e* 293 (26.19), 263 (97.51), 261 (100), 135 (61.75), 91 (64.94), 57 (66.76). Anal. Calcd for $C_{22}H_{29}OSiBr$: C, 63.30; H, 7.00. Found: C, 63.27; H, 6.77. Similarly, bromides **15**, **19**, **22**, **24**, and **27** were prepared in 42–70% overall yields from the corresponding aldehydes (see supplementary material).

Reactions of Achiral Aldehydes with the Allylic Bromides 13, 19, and 24. (1*R*/*S*,2*S*/*R*,3*S*)-4-*O*-((*tert*-Butyldiphenyl)silyl)-3-methyl-1-phenyl-2-vinylbutane-1,4-diol (28/29). According to the general procedure described above, benzaldehyde (0.95 g, 8.95 mmol, 1.5 equiv) and **13** (2.50 g, 5.99 mmol) were treated with a suspension of $CrCl_3$ (2.56 g, 16.2 mmol) and $LiAlH_4$ (0.31 g, 8.17 mmol) in THF (100 mL) to provide after column chromatography (hexane/ethyl acetate (5:1)) **28/29** (1.80 g, 68%) as a colorless oil in a diastereomeric mixture (ratio 83:17). which was separated by HPLC (0.8% 2-propanol in hexane). **28**: $[\alpha]^{20}_D$ +11.4 (*c* 1.1, $CHCl_3$); IR (film) ν_{max} 3440, 3070, 3030, 3000, 2960, 2930, 2900, 2860, 1470, 1460, 1450, 1425, 1390, 1360, 1190, 1110, 1090, 1030, 1000, 915, 820, 800, 765, 740, 700, 615, 505 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.73 (d, 3 H, *J* = 7.5 Hz, CH_3), 1.02 (s, 9 H, *t*-$BuCH_3$), 1.58 (m, 1 H, H-3), 2.42 (s, 1 H, OH), 2.77 (ddd, 1 H, *J* = 10, 9.5 Hz, H-2), 3.38 (m, 2 H, H-4), 4.64 (d, 1 H, H-1), 5.14 (dd, 1 H, *J* = 17.5, 2 Hz, vinylic-CH_2), 5.24 (dd, 1 H, *J* = 10, 2 Hz, vinylic-CH_2), 5.78 (ddd, 1 H, *J* = 17.5, 10, 10 Hz, vinylic-CH), 7.20–7.67 (m, 15 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.94, 19.17, 26.81, 35.76, 52.95, 66.93, 74.44, 120.11, 126.96, 127.54, 128.26, 129.46, 129.50, 133.62, 133.67, 135.46, 135.50, 135.55, 142.66; MS (EI, 90 °C) *m/e* 198 (100), 171 (47.09). Anal. Calcd for $C_{29}H_{36}O_2Si$; C, 78.33; H, 8.16. Found: C, 78.03; H, 8.18.

(1*S*,2*R*,3*S*)-Isomer 29: ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (d, 3 H, *J* = 7 Hz, CH_3), 1.05 (s, 9 H, *t*-$BuCH_3$), 1.92 (m, 1 H, H-3), 2.29 (ddd, 1 H, *J* = 10, 5, 5 Hz, H-2), 3.24 (s, 1 H, OH), 3.44 (dd, 1 H, *J* = 11, 5 Hz, H-4), 3.59 (dd, 1 H, *J* = 11, 7.5 Hz, H-4), 4.85 (dd, 1 H, *J* = 17, 2.5 Hz, vinylic-CH_2), 4.90 (d, 1 H, H-1), 5.11 (dd, 1 H, *J* = 10, 2.5 Hz, vinylic-CH_2), 5.85 (ddd, *J* = 17, 10, 10 Hz, vinylic-CH), 7.34 and 7.65 (each mc, 15 H, aryl-H).

(3*S*,4*S*,5*S*/*R*,6*R*/*S*)-1,3-Di-*O*-benzyl-4-methyl-6-phenyl-5-vinylhexane-1,3,6-triol (32/33). According to the general procedure, benzaldehyde (2.81 g, 26.5 mmol, 1.8 equiv) and **19** (5.93 g, 14.7 mmol) were treated with a suspension of $CrCl_3$ (6.28 g, 39.7 mmol) and $LiAlH_4$ (0.75 g, 19.8 mmol) in THF (200 mL) to provide after column chromatography (hexane/ethyl acetate (3:1)) **32/33** (4.32 g, 68%) (ratio 93:7): colorless oil. Major diastereomer **32**: IR (film) ν_{max} 3450, 3065, 3030, 2970, 2930, 2870, 1495, 1450, 1360, 1205, 1090, 1025, 1000, 915, 765, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (d, 3 H, *J* = 7 Hz, CH_3), 1.76 (mc, 3 H, H-2, H-4), 2.48 (ddd, 1 H, *J* = 10, 8, 5 Hz, H-5), 2.48 (d, 1 H, *J* = 2.5 Hz, OH), 3.40 (mc, 3 H, H-1, H-3), AB system (δ_A = 4.21, δ_B = 4.27, 2 H, J_{AB} = 11.5 Hz, benzyl-CH_2), AB system (δ_A = 4.35, δ_B = 4.41, 2 H, J_{AB} = 11.5 Hz, benzyl-CH_2), 4.62 (dd, 1 H, *J* = 8, 2.5 Hz, H-6), 5.12 (dd, 1 H, *J* = 17.5, 2 Hz, vinylic-CH_2), 5.21 (dd, 1 H, *J* = 10, 2 Hz, vinylic-CH_2), 5.82 (ddd, 1 H, *J* = 17.5, 10, 10 Hz, vinylic-CH), 7.25 (mc, 15 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.18, 30.93, 35.83, 53.37, 66.96, 71.75, 72.87, 73.97, 79.79, 119.55, 126.80–128.27, 136.41, 138.47, 138.55, 142.56; MS (EI, 60 °C) *m/e* 107 (15.4), 91 (100, $[C_7H_7]^+$), 77 (8.32, $[C_6H_5]^+$). Anal. Calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.60; H, 7.94.

(2*R*,3*S*,4*S*,5*S*/*R*,6*R*/*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-methyl-6-phenyl-5-vinylhexane-1,2,3,6-tetrol (36/37). According to the general procedure, benzaldehyde (0.76 g, 7.16 mmol) and **24** (1.80 g, 4.87 mmol) were treated with a suspension of $CrCl_3$ (2.0 g, 13 mol) and $LiAlH_4$ (0.25 g, 6.6 mmol) in THF (70 mL) to give after column chromatography (hexane/ethyl acetate (3:1)) **36/37** (1.45 g, 75%) as a colorless oil in a diastereomeric ratio of 96:4. **36**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (d, 3 H, *J* = 7 Hz, CH_3), 1.30 and 1.33 (each s, each 3 H, acetonide), 1.56 (m, 1 H, *J* = 7.5, 4.5 Hz, H-4), 2.30 (d, 1 H, *J* = 2.5 Hz, OH), 2.76 (ddd, 1 H, *J* = 10, 7.5, 4.5 Hz, H-5), 3.56 (dd, 1 H, *J* = 7.5, 4.5 Hz, H-3) 3.72 (dd, 1 H, *J* = 9, 8 Hz, H-1), 3.82 (dd, 1 H, *J* = 9, 7 Hz, H-1), 4.14 (ddd, 1 H, *J* = 8, 7, 4.5 Hz, H-2), AB system (δ_A = 4.48, δ_B = 4.72, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 4.62 (dd, 1 H, *J* = 7.5, 2.5 Hz, H-6), 5.00 (dd, 1 H, *J* = 17.5, 2 Hz, vinylic-CH_2), 5.21 (dd, 1 H, *J* = 10, 2 Hz, vinylic-CH_2), 5.76 (ddd, 1 H, *J* = 17.5, 10, 10 Hz, vinylic-CH), 7.26 (mc, 10 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.20, 25.38, 26.31, 35.80, 52.41, 65.44, 73.52, 74.41, 76.71, 80.32, 108.58, 119.97, 126.75–128.15, 135.88, 138.85, 142.45. Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.72; H, 8.13. Found: C, 75.98; H, 8.17.

(2*R*,3*S*,4*S*,5*S*/*R*,6*S*/*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-methyl-5-vinylnonadecane-1,2,3,6-tetrol (38/39). According to the general procedure, tetradecanal (6.29 g, 29.6 mmol) and allylic bromide **24** (7.29 g, 19.7 mmol) were treated with a suspension of $CrCl_3$ (8.44 g, 53.3 mmol) and $LiAlH_4$ (1.01 g, 26.6 mmol) in THF (300 mL) to give after purification by column chromatography (hexane/ethyl acetate (10:1)) **38/39** (5.94 g, 60%) (ratio 96:4): colorless oil. Major diastereomer **38**: $[\alpha]^{20}_D$ +8.3 (*c* 0.89, $CHCl_3$); IR (film) ν_{max} 3490, 2920, 2850, 1450, 1375, 1365, 1250, 1205, 1155, 1140–970, 910, 850, 730, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 7 Hz, H-19), 0.91 (d, 3 H, *J* = 7 Hz, C-4-CH_3), 1.14–1.50 (m, 24 H, H-7-18), 1.36 and 1.40 (each s, each 3 H, acetonide), 1.54 (d, 1 H, OH), 1.94 (m, 1 H, H-4), 2.37 (ddd, 1 H, *J* = 10, 5, 5 Hz, H-5), 3.68 (mc, 2 H, H-3, H-6), 3.92 (t, 1 H, *J* = 8, 8 Hz, H-1), 4.03 (dd, 1 H, *J* = 8, 6 Hz, H-1), 4.26 (ddd, 1 H, *J* = 8, 6, 5 Hz, H-2), AB system (δ_A = 4.59, δ_B = 4.80, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 5.05 (dd, 1 H, *J* = 17.5, 2 Hz, vinylic-CH_2), 5.23 (dd, 1 H, *J* = 10, 2 Hz, vinylic-CH_2), 5.73 (ddd, 1 H, *J* = 17.5, 10, 10 Hz, vinylic-CH), 7.33 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.88, 14.06, 22.44–35.91, 25.38, 25.53, 50.99, 66.07, 71.41, 73.45, 76.53, 80.20, 108.66, 119.02, 127.44–128.27, 136.39, 138.82; MS (EI, 100 °C) *m/e* 91 (100, $[C_7H_7]^+$). Anal. Calcd for $C_{32}H_{54}O_4$: C, 76.45; H, 10.83. Found: C, 76.18; H, 10.74.

Minor diastereomer **39** (4% of the combined yield, separated by HPLC (1% 2-propanol in hexane)): ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (t, 3 H, *J* = 7 Hz, H-19), 1.06 (d, 3 H, *J* = 7 Hz, C-4-CH_3), 1.18–1.49 (m, 24 H, [C-7–C-18]-CH_2), 1.34 and 1.38 (each s, each 3 H, acetonide), 1.56 (s, 1 H, OH), 2.15 (m, 2 H, H-4, H-5), 3.69 (dd, 1 H, *J* = 5.5, 3 Hz, H-3), 3.80 (m, 1 H, H-6), 3.84 (dd, 1 H, *J* = 8, 8 Hz, H-1), 4.04 (dd, 1 H, *J* = 8, 5.5 Hz, H-1), 4.20 (ddd, 1 H, *J* = 8, 7.5, 5 Hz, H-2),

AB system (δ_A = 4.56, δ_B = 4.61, 2 H, J_{AB} = 10.5 Hz, benzyl-CH_2), 5.08 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.26 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2). 5.75 (ddd, 1 H. J = 17.5, 10, 10 Hz, vinylic-CH), 7.32 (mc, 5 H, aryl-H).

(3*S*,4*S*,5*S*,6*R*)-4-Methyl-6-phenyl-5-vinylhexane-1,3,6-triol (44). The diastereomeric mixture of **32**/**33** (1.50 g, 3.48 mmol) in THF (75 mL) was added to ammonia (75 mL) under vigorous stirring at −40 °C. Sodium chips were added, until the solution became a deep blue color. After stirring for an additional 30 min, powdered NH_4Cl was added, until the mixture became colorless. Warming up to 22 °C under evaporation of the ammonia (ca. 3 h), followed by filtration over a pad of Celite and concentration of the filtrate furnished after purification by column chromatography (ethyl acetate) and recrystallization from diisopropyl ether **44** (0.79 g, 91%) in a diastereomeric purity of >99%. Colorless needles; mp 99 °C; $[\alpha]^{20}_D$ +47.5 (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max} 3200, 3070, 3030, 2970, 2880, 1740, 1490, 1450, 1420, 1375, 1350, 1325, 1290, 1230, 1180, 1135, 1080, 1050, 1020, 990, 935, 910, 860, 820, 760, 720, 700, 680, 640, 580, 525 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (d, 3 H, CH_3), 1.52 (mc, 2 H, H-2), 1.72 (ddq, 1 H, J = 5 Hz, H-4), 2.37 (ddd, 1 H, J = 10, 5, 5 Hz, H-5), 2.97 (t, 1 H, J = 5 Hz, OH), 3.49 (s, 1 H, OH), 3.57 (s, 1 H, OH), 3.94 (mc, 2 H, H-1), 3.99 (dt, 1 H, H-3), 4.82 (d, 1 H, J = 5 Hz, H-6), 4.94 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.15 (dd, 1 H. J = 10, 2 Hz, vinylic-CH_2), 5.98 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.27 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.02, 35.78, 40.51, 55.44, 62.04, 72.74, 73.26, 119.02, 126.45, 127.33, 128.14, 136.51, 142.86; MS (EI, FAB) *m/e* 501 (1.76, $[2M + H]^+$), 251 (12.63, $[M + H]^+$), 233 (100), 159 (22.3), 131 (24.81), 107 (26.19), 105 (27.26), 93 (20.28), 91 (24.9). Anal. Calcd for $C_{15}H_{22}O_3$: C. 71.97; H, 8.86. Found: C, 71.83; 8.72.

Double Stereodifferentiation: Matched Combinations. (2*S*,3*S*,4*R*,5*S*,2′*R*/*S*)-1-*O*-((*tert*-Butyldiphenyl)silyl)-2-methyl-5-*O*-tetrahydropyranyl-3-vinylhexane-1,4,5-triol (52a). According to the general procedure described above, (*S*)-**48a** (1.42 g, 8.98 mmol) and **13** (2.50 g, 5.99 mmol) in THF (30 mL each) were treated with a suspension of $CrCl_3$ (2.65 g, 16.7 mmol) and $LiAlH_4$ (0.31 g, 8.17 mmol) in THF (100 mL) to give after column chromatography (hexane/ethyl acetate (3:1)) **52a** (1.84 g, 62%) as a colorless oil: IR (film) ν_{max} 3470, 3070, 3050, 2940, 2860, 1470, 1425, 1390, 1360, 1260, 1200, 1185, 1110, 1075, 1025, 995, 935, 915, 870, 820, 740, 700, 615, 505 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 6 H, J = 7 Hz, C-2-CH_3), 1.06 (s, 18 H, *t*-BuCH_3), 1.17 (d, 3 H, J = 6 Hz, H-6), 1.31 (d, 3 H, J = 6 Hz, H-6), 1.44−1.93 (m. 14 H, THP-H-3′, -4′. -5′, H-2), 2.45 (mc, 2 H, OH, H-3), 2.56 (mc, 2 H, OH, H-3), 3.48 (mc, 6 H, H-5, H-1), 3.82 (m, 2 H, H-4), 3.92 (m, 4 H, THP-H-6′), 4.69 (m, 2 H, THP-H-2′), 5.16 (m, 4 H, J = 17.5, 10, 2 Hz, vinylic-CH_2), 6.20 (m, 2 H, J = 17.5, 10 Hz, vinylic-CH), 7.39 (m, 12 H, aryl-H), 7.66 (m, 8 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.10, 12.74, 13.11, 15.86, 19.17, 19.84, 25.44, 26.83, 31.16, 35.87. 36.03, 46.67, 47.68, 62.78, 62.91, 66.90, 67.05, 72.73, 72.89, 73.68, 74.87, 96.86, 98.65, 118.35, 118.51, 127.65, 129.65, 133.52, 135.52, 135.61, 135.93, 136.37; MS (EI, 180 °C) *m/e* 337 (30.39), 199 (79.72), 85 (100). Anal. Calcd for $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.92. Found: C, 72.28; H, 8.62.

(2*S*,3*S*,4*R*,5*S*)-1-*O*-((*tert*-Butyldiphenyl)silyl)-2-methyl-3-vinylhexane-1,4,5-triol (52b). To a stirred solution of **52a** (1.43 g, 2.88 mmol) in MeOH (200 mL) was added PPTS until the pH was well below 3.5. After stirring for 24 h at 22 °C, the mixture was neutralized with powdered $NaHCO_3$ and concentrated. Dilution with ether (100 mL), drying ($MgSO_4$), and filtration furnished after purification by column chromatography (hexane/ethyl acetate (1:1)) **52b** (0.64 g, 54%): white crystals; mp 40 °C; $[\alpha]^{20}_D$ −1.7 (*c* 1.05, $CHCl_3$); IR (KBr) ν_{max} 3420, 3070, 3050, 2960, 2930, 2900, 2860, 1470, 1425, 1390, 1360, 1110, 1085, 1060, 1005, 1000, 985, 920, 825, 810, 740, 700, 615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, 3 H, J = 7 Hz, C-2-CH_3), 1.07 (s, 9 H, *t*-BuCH_3), 1.24 (d. 3 H. J = 6 Hz. H-6). 1.84 (m. 1 H, H-2), 2.07 (d, 1 H, J = 6 Hz, OH), 2.40 (ddd, 1 H, J = 10, 5, 5 Hz, H-3), 2.60 (d, 1 H, J = 4 Hz, OH). 3.50 (m, 2 H, H-1), 3.71 (m, 1 H, H-5), 3.82 (m, 1 H, H-4), 5.14 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.20 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.80 (ddd, 1 H, J = 17.5, 10, 10 Hz. vinylic-CH), 7.38 (mc, 6 H, aryl-H). 7.63 (mc, 4 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.32, 17.75, 19.13, 26.78, 35.91, 48.70, 67.19, 68.53, 74.17, 118.92, 127.67, 129.71, 133.28, 135.48, 135.59, 136.51; MS (EI, 140 °C) *m/e* 199 (100), 139 (23.97), 57 (50.95), 55 (41.04). Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79. Found: C, 72.31; H, 8.38.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*)-3-*O*-Benzyl-7-*O*-((*tert*-Butyldimethyl)silyl)-1,2-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (53a). According to the general procedure, **24** (3.47 g, 9.40 mmol) and (*S*)-**48b** (1.98 g, 10.58 mmol) in THF (40 mL each) were treated with a suspension of $CrCl_3$ (4.0 g, 25.3 mmol) and $LiAlH_4$ (0.48 g, 12.7 mmol) in THF (100 mL) to give after column chromatography (hexane/ethyl acetate (5:1)) **53a** (3.24 g, 72%); colorless oil: $[\alpha]^{20}_D$ +10.8 (*c* 2.4, $CHCl_3$); IR (film) ν_{max} 3570, 3035, 3015, 2980, 2950, 2930, 2885, 2860, 1495, 1469, 1460, 1450, 1420, 1375, 1367, 1348, 1290, 1252, 1210, 1152, 1123, 1075, 1025, 1004, 967, 938, 912, 872, 833, 775, 732, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 and 0.11 (each s, each 3 H, Si-CH_3), 0.90 (d, 3 H, J = 7.5 Hz, C-4-CH_3), 0.93 (s, 9 H, *t*-BuCH_3), 1.08 (d, 3 H, J = 6.5 Hz, H-8), 1.36 and 1.42 (each s, each 3 H, acetonide), 1.84 (m, 1 H, H-4), 2.36 (d, 1 H, OH), 2.61 (m, 1 H, H-5), 2.60−4.30 (m, 6 H, H-1, -2, -3, -6, -7), AB system (δ_A = 4.59, δ_B = 4.91, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 5.06 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.22 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.80 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.32 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −4.82, −4.28, 12.41, 17.01, 17.97, 25.39, 25.80, 26.40, 36.59, 46.22, 65.05, 69.75, 74.11, 74.83, 77.13, 79.57, 108.54, 118.49, 127.34, 127.41, 128.22, 136.14, 138.91; MS (CI, 50 °C) *m/e* 478 (2, $[M]^+$), 463 (21, $[M - CH_3]^+$), 363 (83), 313 (68), 91 (100, $[C_7H_7]^+$). Anal. Calcd for $C_{27}H_{46}O_5Si$: C, 67.74; H, 9.69. Found: C, 67.99; H, 9.70.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (53b). To a stirred solution of **53a** (10 g, 21 mmol) in THF (300 mL) was added Bu_4NF(trihydrate) (10.3 g, 33 mmol) in THF (25 mL) dropwise at 22 °C, and stirring was continued for 1 h. Water (100 mL) was added, and the mixture was concentrated. Dilution and extraction with ether (200 mL each), followed by drying ($MgSO_4$) of the combined organic phases, furnished after concentration and purification of the residue by column chromatography (hexane/ethyl acetate (1:1)) **53b** (6.9 g, 90%): colorless oil; $[\alpha]^{20}_D$ +33.7 (*c* 2.5, $CHCl_3$); IR (film) ν_{max} 3650−3150, 3075, 3035, 2980, 2940, 2890, 2650−2400, 1640, 1500, 1355, 1420, 1378, 1368, 1350, 1325, 1295, 1248, 1212, 1157, 1120, 1060, 1028, 1005, 980, 920, 860, 790, 760, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.19 (d, 3 H, J = 7 Hz, H-8), 1.39 and 1.45 (each s, each 3 H, acetonide), 1.78 (m, 1 H, H-4), 2.50 (s, 2 H, OH), 2.59 (ddd, 1 H, J = 10, 5, 5 Hz, H-5), 3.52−4.34 (m, 6 H, H-1, -2, -3, -6, -7), AB system (δ_A = 4.58, δ_B = 4.86, 2 H, J_{AB} = 11.5 Hz, benzyl-CH_2), 5.09 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.25 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.81 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.33 (m, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.70, 18.93, 25.45, 26.50, 37.70, 48.12, 66.49, 68.53, 74.06, 78.33, 82.03, 109.50, 118.20, 127.20, 127.50, 128.23, 136.29, 138.37; MS (CI, 160 eV, 130 °C) *m/e* 365 (24), 289 (30), 199 (35), 181 (30), 155 (60), 91 (56, $[C_7H_7]^+$). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.88; H, 8.88.

(2*R*,3*R*,4*R*,5*R*,6*S*,7*R*)-3-*O*-Benzyl-7-*O*-((*tert*-butyldimethyl)silyl)-1,2-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (54a). According to the general procedure, allylic bromide **27** (2.95 g, 7.99 mmol) and (*R*)-**48b** (2.13 g, 11.37 mmol) were treated with a suspension of $CrCl_3$ (3.42 g, 21.6 mmol) and $LiAlH_4$ (0.41 g, 10.8 mmol) in THF (100 mL) to give after column chromatography (hexane/ethyl acetate (5:1)) **54a** (2.10 g, 55%): colorless oil; $[\alpha]^{20}_D$ +24.6 (*c* 1.30, $CHCl_3$); IR and MS data see **53a**; ^1H NMR (250 MHz, $CDCl_3$) δ 0.08 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.89 (s, 9 H, *t*-BuCH_3), 0.95 (d, 3 H, J = 7.5 Hz, C-4-CH_3), 1.11 (d, 3 H, J = 6.25 Hz, H-8), 1.38 and 1.46 (each s, each 3 H, acetonide), 1.81−1.94 (m, 1 H, H-4), 2.60 (ddd, 1 H, J = 8, 7, 6 Hz, H-5), 2.84 (s, 1 H, OH), 3.33 (dd, 1 H, J = 6, 5 Hz, H-3), 3.58 (dd, 1 H, J = 8, 6 Hz, H-6), 3.72 (dd, 1 H, J = 7.5, 7 Hz, H-1), 3.84 (dq, 1 H, J = 8, 6.25 Hz, H-7), 4.03 (dd, 1 H, J = 7, 7.5 Hz, H-1), 4.31 (ddd, 1 H, J = 7.5, 7, 6 Hz, H-2), AB system (δ_A = 4.64, δ_B = 4.81, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 5.10 (dd, 1 H, J = 16, 2.5 Hz, vinylic-CH_2), 5.25 (dd, 1 H, J = 10, 2.5 Hz, vinylic-CH_2), 5.89 (ddd, 1 H, J = 16, 10, 8 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −4.64, −4.14, 13.98, 17.95. 25.50, 25.93, 26.57, 37.93, 46.65, 66.58, 70.12, 74.27, 75.16, 78.06, 82.64, 108.94, 118.18, 127.49, 127.78, 128.29, 136.99, 138.90; HRMS Calcd for $C_{27}H_{46}O_5Si$ ($[M]^+$) 478.31145, found 478.31143.

(2*R*,3*R*,4*R*,5*R*,6*S*,7*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (54b). According to the procedure described above for the desilylation of **53a**, **54a** (2.0 g, 4.18 mmol) was treated with Bu_4NF(trihydrate) (2.06 g, 6.5 mmol) in THF (50 mL). Usual workup gave after purification by column chromatography (hexane/ethyl acetate (1:1)) **54b** (1.37 g, 90%) as a colorless oil; $[\alpha]^{20}_D$ +26.7 (*c* 1.0, $CHCl_3$); IR and MS data see **53b**; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, 3 H, J = 7.5 Hz, CH_3), 1.18 (d, 3 H, J = 6.5 Hz, H-8), 1.37 and 1.46 (each s, each 3 H, acetonide), 1.84−1.96 (m, 1 H, H-4), 2.17 (s, 2 H, OH), 2.56 (ddd, 1 H, J = 8.5, 6.5, 6.5 Hz, H-5), 3.31 (dd, 1 H, J = 7, 5.5 Hz, H-3), 3.65 (dd, 1 H, J = 6.5, 5.5 Hz, H-6), 3.71 (dd, 1 H. J = 8, 8 Hz, H-1), 3.75−3.85 (m, 1 H, H-7), 4.03 (dd, 1 H, J = 8, 6.5 Hz, H-1), 4.31 (ddd, 1 H, J = 8, 7, 6.5 Hz, H-2), AB system (δ_A = 4.61. δ_B = 4.81, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 5.11 (dd, 1 H, J = 16.5, 2 Hz, vinylic-CH_2), 5.27 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.90 (ddd, 1 H, J = 16.5, 10, 8.5 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.79, 17.53, 25.38, 26.44, 37.19, 47.63, 66.29, 68.71, 73.90. 74.20, 77.76, 82.28, 108.84, 119.25, 127.54, 127.66,

128.28, 136.84, 138.39; HRMS calcd for $C_{20}H_{29}O_5$ ($[M - CH_3]^+$) 349.20150, found 349.20156.

(2*S*,3*S*,4*R*,5*S*)-1-*O*-((*tert*-Butyldiphenyl)silyl)-4,5-*O*-isopropylidene-2-methyl-3-vinylhexane-1,4,5-triol (55). To a stirred solution of diol **52b** (0.41 g, 0.99 mmol) in CH_2Cl_2 (50 mL) was added PPTS until the pH became about 4. DMP (0.16 g, 1.5 mmol) was added, and the solution continued to be stirred for 1 h at 22 °C. The mixture was poured into a saturated aqueous $NaHCO_3$ solution (50 mL), and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate (3:1)) to give **55** (0.44 g, 98%): colorless oil; $[\alpha]^{20}_D$ −25.1 (*c* 2.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, 3 H, J = 7 Hz, CH_3), 1.05 (s, 9 H, *t*-$BuCH_3$), 1.20 (d, 3 H, J = 6.5 Hz, H-6), 1.32 and 1.44 (each s, each 3 H, acetonide), 1.74 (m, 1 H, H-2), 2.73 (m, 1 H, H-3), 3.40 (dd, 1 H, J = 10, 6.5 Hz, H-1), 3.48 (dd, 1 H, J = 10, 8.5 Hz, H-1), 4.18 (mc, 2 H, H-4, H-5), 5.08 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.14 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.69 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.36 (m, 6 H, aryl-H), 7.68 (m, 4 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.50, 16.23, 19.18, 25.98, 26.85, 28.52, 36.63, 42.85, 66.52, 73.85, 78.50, 107.39, 117.92, 127.60, 129.56, 129.60, 133.75, 135.32, 135.50, 135.59; MS (EI, 90 °C) *m/e* 199 (100), 183 (24), 115 (53.48), 69 (70.25), 59 (33.62), 43 (67.58). Anal. Calcd for $C_{28}H_{40}O_3Si$: C, 74.29; H, 8.91. Found: C, 74.21; H, 9.11.

(2*R*,3*S*,4*S*,5*S*,6*R*,7*S*)-3-*O*-Benzyl-1,2:6,7-di-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (56a). Ketalization of **53b** (8.0 g, 22 mmol) was accomplished with DMP (3.5 g, 34 mmol) as described for the preparation of **55** to give after purification by column chromatography (hexane/ethyl acetate (5:1)) **56a** (7.8 g, 88%) as a colorless oil: $[\alpha]^{20}_D$ −27.4 (*c* 1.8, $CHCl_3$); IR (film) ν_{max} 3070, 3030, 2980, 2935, 2885, 1495, 1450, 1380. 1350, 1300, 1240, 1215, 1170, 1160, 1119, 1065, 1038, 1028, 1008, 970, 931, 915, 870, 860, 850, 790, 750, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 7 Hz, CH_3), 1.13 (d, 3 H, J = 7 Hz, H-8), 1.30, 1.35, 1.39, and 1.42 (each s, each 3 H, acetonides), 1.45 (m, 1 H, H-4), 2.79 (m, 1 H, H-5), 3.65 (dd, 1 H, J = 9, 3 Hz, H-6), 3.95 (dd, 1 H, J = 9, 7.5 Hz, H-1), 3.99 (dd, 1 H, J = 9, 9 Hz, H-1), 4.10 (dd, 1 H, J = 9, 6 Hz, H-3), 4.18 (ddd, 1 H, J = 9, 7.5 Hz, H-2), 4.28 (dq, 1 H, J = 7, 3 Hz, H-7), AB system (δ_A = 4.60, δ_B = 4.98, 2 H, J_{AB} = 11.5 Hz, benzyl-CH_2), 5.00 (dd, 1 H, J = 17, 2 Hz, vinylic-CH_2), 5.20 (dd. 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.78 (ddd, 1 H, J = 17, 10, 9 Hz, vinylic-CH), 7.30 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.73, 15.68, 25.16, 25.53, 26.08, 27.96, 37.70, 42.91, 64.12, 73.71, 74.18, 77.09, 78.29, 78.82, 107.01, 108.27, 117.99, 127.05, 127.13, 127.93. 135.48, 138.60; MS (CI, 20 °C) *m/e* 405 (12.4, $[MH]^+$), 289 (100), 239 (34.3), 91 (75.75 $[C_7H_7]^+$); HRMS calcd for $C_{23}H_{33}O_5$ ($[M - CH_3]^+$) 389.2328, found 389.2329.

(2′*R*,2″*S*,3*S*,4*S*,5*R*)-4-(Benzyloxy)-2-((2′,2″-isopropylidenedioxy)propyl)-3-methyl-5,6-(isopropylidenedioxy)hexanal (56b). **56a** (5.0 g, 12.4 mmol) was dissolved in CH_2Cl_2 (300 mL), and at −78 °C ozone was passed through the solution until it became slightly blue. Excess ozone was removed with a stream of nitrogen (solution became colorless), and PPh_3 (13 g, 50 mmol) was added. The mixture was warmed up to 22 °C during 5 h, followed by evaporation of the solvent under reduced pressure and dilution of the residue with ether (200 mL). The precipitated PPh_3O was separated by filtration, and the filtrate was concentrated. Purification of the residue by column chromatography (hexane/ethyl acetate (3:1)) gave **56b** (4.3 g, 85%): colorless oil; $[\alpha]^{20}_D$ +4.2 (*c* 2.1, $CHCl_3$): IR (film) ν_{max} 3065, 3030, 2980, 2930, 2880, 2720, 1720, 1595, 1450, 1375, 1370, 1350, 1300, 1245, 1215, 1170, 1160, 1115, 1065, 1025, 1010, 855, 745, 700 cm^{-1}: ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (d, 3 H, J = 7 Hz, C-3-CH_3), 1.17 (d, 3 H, J = 6.5 Hz, C-2″-CH_3), 1.31, 1.33, 1.37 and 1.40 (each s. each 3 H, acetonides), 2.02, 2.86, 3.62, 3.80. 4.02, 4.18–4.34, 4.46 (each m, 8 H, H-2-6, H-2′, H-2″), AB system (δ_A = 4.63, δ_B = 4.71, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 7.31 (mc, 5 H, aryl-H), 9.78 (d, 1 H, J = 4 Hz, CHO); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.46, 15.81, 25.27, 25.61, 26.50, 27.90, 36.57, 50.33, 66.41, 73.59, 74.55, 76.07, 76.50, 81.82, 108.03, 108.96, 127.67, 127.73, 128.33, 139.10, 203.14; MS (CI, 40 °C) *m/e* 406 (1), 391 (1), 91 (100). Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.96; H, 8.43. Found: C, 68.05; H, 8.57.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*S*)-3-*O*-Benzyl-1,2:6,7-di-*O*-isopropylidene-5-(hydroxymethyl)-4-methyloctane-1,2,3,6,7-pentol (56c). To a stirred suspension of $LiAlH_4$ (0.30 g. 7.90 mmol) in diethyl ether (50 mL) was added **56b** (5.0 g, 12 mmol) in ether (150 mL) dropwise at 0 °C. After stirring for 3 h at 22 °C, saturated aqueous $MgSO_4$ solution (1.5 mL) and powdered K_2CO_3 (70 mg, 0.5 mmol) were added, and the mixture continued to be stirred for 4 h. Filtration over a pad of Celite, followed by drying ($MgSO_4$), evaporation of volatiles, and purification of the residue by column chromatography (hexane/ethyl acetate (3:1)) gave **56c** (4.65 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ −14.1 (*c* 2.1, $CHCl_3$): IR (film) ν_{max} 3050, 2980. 2934, 2883. 1735, 1494, 1450, 1375, 1370. 1350, 1300, 1240, 1215, 1171, 1160, 1145, 1100, 1060, 1045, 1025, 1005, 990, 940, 860, 850, 750, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.14 (d, 3 H, J = 6.5 Hz, H-8), 1.32, 1.34, 1.39, and 1.43 (each s, each 3 H, acetonides), 1.61 (m, 1 H, H-4), 2.25 (m, 1 H, H-5), 3.20 (dd, 1 H, J = 5 Hz, OH), 3.63–4.31 (m, 8 H, H-1, -2, -3, -5′, -6, -7), AB system (δ_A = 4.65, δ_B = 4.78, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 7.30 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.94, 15.55, 25.12, 25.71, 26.26, 28.21, 35.54, 39.01, 61.15, 65.66, 73.85, 75.08, 76.32, 79.52, 81.90, 107.35, 108.51, 127.41, 127.48, 128.06, 137.76; MS (EI, 50 °C) *m/e* 408 (1), 393 (1), 91 (100, $[C_7H_7]^+$). Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.88; H, 8.40.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*S*)-3-*O*-Benzyl-1,2:6,7-di-*O*-isopropylidene-4-methyl-5-*O*-((methylsulfonyl)methyl)octane-1,2,3,6,7-pentol (56d). To a stirred solution of **56c** (2.6 g, 6.4 mmol) in CH_2Cl_2 (100 mL) were added NEt_3 (1 g, 10 mmol) and CH_3SO_2Cl (0.8 g, 7 mmol) dropwise at 0 °C. After stirring for 24 h at 22 °C, brine (40 mL) was added, the organic layer was separated, and the aqueous one was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to furnish after column chromatography (hexane/ethyl acetate (1:1)) **56d** (2.2 g, 71%) as an unstable colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.10 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.15 (d, 3 H. J = 7 Hz, H-8), 1.31, 1.37, 1.41, and 1.43 (each s, each 3 H, acetonides), 1.56 (m, 1 H, H-4), 2.49 (m, 1 H, H-5), 2.91 (s, 3 H, S-CH_3), 3.73, 3.91–4.64 (each m, 8 H, H-1, -2, -3, -5′, -6, -7), AB system (δ_A = 4.63, δ_B = 4.89, 2 H, J_{AB} = 11.5 Hz, benzyl-CH_2), 7.34 (mc, 5 H, aryl-H).

(1*S*,2*S*,3*R*,1′*R*,1″*R*,2″*S*)-1-(1′,2′-*O*-Isopropylideneethane-1′,2′-diol-1′-yl)-3-(1″,2″-*O*-isopropylidenepropane-1″,2″-diol-1″-yl)-2-methyltetrahydrofuran (57). To **56d** (2 g, 4 mmol) in MeOH (20 mL) was added *p*-TsOH until the pH became about 3. Concentration of the mixture under reduced pressure and dilution with CH_2Cl_2 (30 mL), followed by addition of DMP (0.62 g, 6.0 mmol), led to spontaneous cyclization of **56d**. Saturated aqueous Na_2SO_4 solution (5 mL) was added; evaporation of volatiles, dilution with ether (100 mL), separation of the organic layer, and drying ($MgSO_4$) gave after column chromatography (hexane/ethyl acetate (3:1)) **57** (0.92 g, 75%); colorless prisms. The material crystallized from *n*-pentane: mp 75 °C; $[\alpha]^{20}_D$ −2.5 (*c* 2.1, $CHCl_3$); IR (KBr) ν_{max} 2980, 2960, 2955, 2915, 2890, 2859, 1485, 1450, 1375, 1365, 1300, 1270, 1243. 1217, 1161, 1100, 1070, 1060, 1040, 1030, 995, 965, 925, 865, 850, 810, 790, 670, 640, 510 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz, C-2-CH_3), 1.24 (d, 3 H, J = 6.5 Hz, H-3″), 1.25, 1.33, 1.39 and 1.40 (each s, each 3 H, acetonides), 2.32 (ddq, 1 H, J = 8, 7, 3.5 Hz, H-2), 2.44 (m, 1 H, H-3), 3.51–4.26 (m, 8 H, H-1, -4, -1′, -2′, -1″, -2″); ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.42, 16.67, 25.24, 25.67, 26.75, 28.29, 36.53, 41.68, 67.29, 71.09, 73.38, 77.10, 77.43, 88.05, 107.30, 109.30; MS (EI, 80 eV, 60 °C) *m/e* 300 (1, $[M]^+$), 285 (5), 199 (31), 141 (63), 97 (39), 57 (100), 43 (92). Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40. Found: C, 64.02, H, 9.42.

(2*R*,3*R*,4*R*,5*R*,6*S*,7*R*)-3-*O*-Benzyl-1,2:6,7-di-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (58). To a stirred solution of diol **54b** (1.1 g, 3.02 mmol) and DMP (0.49 g, 4.7 mmol) in CH_2Cl_2 (50 mL) was added *p*-TsOH until the pH became 3. Workup according to the procedure described above for **55** gave after purification by column chromatography (hexane/ethyl acetate (5:1)) diacetonide **58** (1.03 g, 84%); colorless oil; $[\alpha]^{20}_D$ +64.2 (*c* 1.4, $CHCl_3$); IR and MS data see **56a**; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.16 (d, 3 H, J = 6.5 Hz, H-8), 1.34 and 1.38 (each s, each 3 H, acetonide-CH_3), 1.45 (s, 6 H, acetonide-CH_3), 1.80–1.96 (m, 1 H, H-4), 2.79 (ddd, 1 H, J = 8.5, 2.5 Hz, H-5), 3.27 (dd, 1 H, J = 9, 4 Hz, H-3), 3.83 (dd, 1 H, J = 8, 8 Hz, H-1), 4.03 (dd, 1 H, J = 8, 7 Hz, H-1′), 4.16 (dd, 1 H, J = 8.5, 5.5 Hz, H-6), 4.20–4.32 (m, 2 H, H-2, H-7), AB system (δ_A = 4.65, δ_B = 4.74, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 5.09 (dd, 1 H, J = 16.5, 2 Hz, vinylic-CH_2), 5.26 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.81 (ddd, 1 H, J = 16.5, 10, 8.5 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.58, 16.06, 25.40, 25.94, 26.29, 28.42, 37.81, 42.95, 66.11, 74.09, 74.36, 77.00, 78.78, 80.73, 107.35, 108.63, 118.30, 127.45, 128.28, 136.06, 138.48; HRMS calcd for $C_{23}H_{33}O_5$ ($[M - CH_3]^+$) 389.2328, found 389.2329.

Double Stereodifferentiation; Mismatched Combinations. Compounds **60**, (−)-**61**, **62**, and (+)-**61** are described in ref 22. **(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-3-*O*-Benzyl-7-*O*-((*tert*-butyldimethyl)silyl)-1,2-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (63a).** According to the general procedure, **27** (3.37 g, 9.13 mmol) and (*S*)-**48b** (3.04 g, 16.3 mmol) in THF (50 mL each) were treated with a suspension of $CrCl_3$ (3.91 g, 24.7 mmol) and $LiAlH_4$ (0.47 g, 12.4 mmol) in THF (100 mL) at 0 °C to provide after purification by column chromatography (hexane/ethyl acetate (5:1)) **63a** (2.90 g, 66%) as a colorless oil; $[\alpha]^{20}_D$ +28.3 (*c* 1.3, $CHCl_3$); IR and MS see **53a**; ^1H NMR (250 MHz, $CDCl_3$) δ 0.08 and 0.11 (each s, each 3 H, $SiCH_3$), 0.91 (s, 9 H, *t*-$BuCH_3$), 1.01 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.06 (d, 3 H, J = 6.5 Hz,

H-8), 1.38 and 1.46 (each s, each 3 H, acetonide), 2.00–2.15 (m, 1 H, H-4), 2.31–2.41 (m, 1 H, H-5), 2.59 (s, 1 H, OH), 3.41 (dd, 1 H, J = 7.5, 6 Hz, H-3), 3.42 (m, 1 H, H-6), 3.67 (dq, 1 H, J = 6.5, 4 Hz, H-7), 3.75 (dd, 1 H, J = 8, 8 Hz, H-1), 4.05 (dd, 1 H, J = 8, 6 Hz, H-1), 4.35 (ddd, 1 H, J = 8, 8, 6 Hz, H-2), AB system (δ_A = 4.64, δ_B = 4.77, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 4.96 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.15 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.84 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ -4.80, -4.11, 15.01, 17.98, 19.35, 25.60, 25.84, 26.56, 37.24, 46.43, 66.49, 70.81, 73.41, 77.62, 82.11, 108.81, 117.74, 127 28, 127.58, 128.14, 136.34, 139.02; HRMS calcd for $C_{27}H_{46}O_5Si$ ([M]$^+$) 478.31145, found 478.31143.

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (63b). According to the desilylation described above for **53a**, silyl ether **63a** (2.0 g, 4.2 mmol) was treated with Bu_4NF(trihydrate) (2.06 g, 6.5 mmol) in THF (100 mL) to give after workup and purification by column chromatography (hexane/ethyl acetate (1:1)) **63b** (1.38 g, 90%) as a colorless oil: IR and MS data see **53b**; $[\alpha]^{20}_D$ +19.8 (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.02 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.14 (d, 3 H, J = 6.5 Hz, H-8), 1.37 and 1.46 (each s, each 3 H, acetonide), 1.89–2.04 (m, 1 H, H-4), 2.29–2.42 (m, 1 H, H-5), 2.38 (d, 1 H, J = 4 Hz, OH), 3.16 (d, 1 H, J = 4 Hz, OH), 3.37 (dd, 1 H, J = 6.5, 5.5 Hz, H-3), 3.46 (ddd, 1 H, J = 5.5, 4, 4 Hz, H-6), 3.60–3.76 (m, 1 H, H-7), 3.68 (dd, 1 H, J = 8, 8 Hz, H-1), 4.06 (dd, 1 H, J = 8, 6.5 Hz, H-1), 4.38 (ddd, 1 H, J = 8, 6.5, 6.5 Hz, H-2), AB system (δ_A = 4.64, δ_B = 4.88, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 5.05 (dd, 1 H, J = 17, 2 Hz, vinylic-CH_2), 5.19 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.92 (ddd, 1 H, J = 17, 10, 8.5 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.73, 18.95, 25.48, 26.57, 37.68, 48.14, 66.42, 68.56, 74.11, 75.11, 78.24, 82.99, 109.02, 118.37, 127.61, 127.84, 128.30, 136.67, 138.37; HRMS calcd for $C_{20}H_{29}O_5$ ([M - CH_3]$^+$) 349.20151, found 349.20156.

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-3-*O*-Benzyl-1,2:6,7-di-*O*-isopropylidene-4-methyl-5-vinyloctane-1,2,3,6,7-pentol (64). To a stirred solution of diol **63b** (1.1 g, 3.02 mmol) in CH_2Cl_2 (50 mL) were added DMP (0.49 g, 4.7 mmol) and p-TsOH at 22 °C until the pH became about 3. Workup as described for the preparation of **55** gave after chromatography (hexane/ethyl acetate (5:1)) **64** (1.0 g, 84%): colorless oil; IR and MS data see **56a**; $[\alpha]^{20}_D$ +30.7 (c 30.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.02 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.19 (d, 3 H, J = 6 Hz, H-8), 1.32, 1.36, 1.38, and 1.46 (each s, each 3 H, acetonides), 2.00 (ddq, 1 H, J = 7.2, 7.2, 4.2 Hz, H-4), 2.48 (ddd, 1 H, J = 10, 4, 3 Hz, H-5), 3.34 (dd, 1 H, J = 7, 5 Hz, H-3), 3.65 (dd, 1 H, J = 8.5, 3 Hz, H-6), 3.76 (dd, 1 H, J = 8, 8 Hz, H-1), 3.82 (dq, 1 H, J = 8.5, 6 Hz, H-7), 4.05 (dd, 1 H, J = 8, 6.5 Hz, H-1), 4.32 (ddd, 1 H, J = 8, 6.5, 5 Hz, H-2), AB system (δ_A = 4.63, δ_B = 4.79, 2 H, J_{AB} = 12 Hz, benzyl-CH_2), 4.96 (dd, 1 H, J = 16, 2 Hz, vinylic-CH_2), 5.11 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.84 (ddd, 1 H, J = 16, 10, 10 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.10, 17.15, 25.40, 26.50, 26.84, 27.33, 38.81, 45.12, 66.34, 73.50, 74.55, 77.64, 81.85, 84.62, 107.61, 108.72, 118.62, 127.48, 128.23, 135.47, 138.87; HRMS calcd for $C_{23}H_{33}O_5$ ([M - CH_3]$^+$) 389.23280, found 389.23293.

(3*S*,4*S*,5*S*,6*R*,7*R*)-1,3-*O*-Benzyl-4-methyl-7-*O*-((*tert*-butyldimethyl)silyl)-5-vinyloctane-1,3,6,7-tetrol (65). According to the general procedure, **19** (1.0 g, 2.48 mmol) and (*R*)-**48b** (0.70 g, 3.74 mmol) were treated with a suspension of $CrCl_3$ (1.06 g, 6.69 mmol) and $LiAlH_4$ (127 mg, 3.35 mmol) in THF (70 mL) to give after column chromatography (hexane/ethyl acetate (5:1)) **65** (1.15 g, 90%) as a colorless oil: $[\alpha]^{20}_D$ -23.1 (c 1.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 6 H, $SiCH_3$), 0.89 (m, 12 H, t-$BuCH_3$, C-4-CH_3), 1.00 (d, 3 H, J = 7 Hz, H-8), 1.79–2.08 (m, 3 H, H-2, H-4), 2.16 (m, 1 H, H-5), 2.52 (s, 1 H, OH), 3.40–3.82 (m, 5 H, H-1, -3, -6, -7), 4.51 (mc, 4 H, benzyl-CH_2), 4.93 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.09 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.76 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.29 (mc, 10 H, aryl-H): ^{13}C NMR (63 MHz, $CDCl_3$) δ -4.77, -4.09, 12.84, 18.03, 19.18, 25.86, 31.73, 36.24, 47.39, 67.60, 71.11, 71.63, 73.03, 75.84, 77.79, 117.01, 127.31, 127.52, 127.69, 128.24, 128.32, 137.19, 138.59, 139.15; MS (EI, 150 °C) m/e 512 (1.26, [M]$^+$), 455 (12.83, [M - t-Bu]$^+$), 131 (100, [OSi-t-$BuMe_2$]$^+$); HRMS; calcd for $C_{27}H_{39}O_4Si$ ([M - t-Bu]$^+$). 455.261762, found 455.261793.

(2*S*,3*R*/*S*,4*R*/*S*,5*R*,2′*R*/*S*)-1-*O*-((*tert*-Butyldiphenyl)silyl)-2-methyl-5-*O*-tetrahydropyranyl-3-vinylhexane-1,4,5-triol (66a). According to the general procedure, allylic bromide **13** (1.0 g, 2.40 mmol) and (*R*)-**48a** (0.57 g, 3.60 mmol) were treated with a suspension of $CrCl_3$ (1.03 g, 6.50 mmol) and $LiAlH_4$ (0.12 g, 3.16 mmol) in THF (50 mL) at 0 °C to give after purification by column chromatography (hexane/ethyl acetate (3:1)) **66a** (0.95 g, 80%) as a colorless oil: IR and MS data see **52a**; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (m, 3 H, J = 7 Hz, C-2-CH_3), 1.05 (s, 9 H, t-$BuCH_3$), 1.22 (mc, 3 H, J = 6 Hz, H-6), 1.42–2.12 (m, 7 H, THP-H-3′, -4′, -5′, H-2), 2.27 (m, 1 H, H-3), 2.61 (d, 1 H, OH), 3.56 (mc, 5 H, THP-H-6′, H-1, H-4, H-5), 3.92 (m, 1 H, THP-H-6′), 4.51 and 4.66 (each m, each 1 H, THP-H-2′), 5.04 (mc, 2 H, vinylic-CH_2), 5.77 (m, 1 H, vinylic-CH), 7.37 (m, 6 H, aryl-H), 7.63 (m, 4 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.82, 16.25, 17.75, 19.32, 20.17, 20.99, 25.16, 25.40, 26.59, 26.95, 31.20, 36.93, 47.23, 63.20, 66.79, 75.60, 78.32, 100.94, 117.66, 127.60, 129.56, 135.61, 135.69, 136.02, 136.31. Anal. Calcd for $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.92. Found: C, 72.42; H, 8.96.

(2*S*,3*R*/*S*,4*R*/*S*,5*R*)-1-*O*-((*tert*-Butyldiphenyl)silyl)-2-methyl-3-vinylhexane-1,4,5-triol (66b). Deprotection of **66a** (0.68 g, 1.37 mmol) with MeOH (100 mL) and PPTS furnished after column chromatography (hexane/ethyl acetate (2:1)) **66b** (0.29 g, 51%) as a colorless oil in a diastereomeric mixture (ratio: 3:1:1): IR and MS data see **52b**; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.80 (d, J = 7 Hz, minor diastereomer CH_3), 0.84 (d, J = 7 Hz, major diastereomer CH_3) 0.85 (d, J = 7 Hz, minor diastereomer CH_3), 1.05 (s, t-$BuCH_3$), 1.14 (d, J = 6 Hz, major diastereomer H-6), 1.24 (d, J = 6 Hz, minor diastereomer H-6), 1.25 (d, J = 6 Hz, minor diastereomer H-6), 1.91 (m, H-2), 2.12 (m, major diastereomer H-3), 2.39 (m, minor diastereomer H-3), 2.66 (m, minor diastereomer OH), 3.28 (d, major diastereomer OH), 3.55 (mc, H-1, 4, 5), 4.98 (m, J = 17.5, 2 Hz, vinylic-CH_2), 5.11 (m, J = 10, 2 Hz, vinylic-CH_2), 5.80 (m, vinylic-CH), 7.37 (m, aryl-H), 7.63 (m, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.27, 15.15, 16.48, 17.69, 18.38, 19.14, 19.29, 26.81, 35.89, 36.84, 37.87, 48.62, 49.63, 66.27, 67.16, 68.48, 68.89, 69.10, 74.17, 75.76, 117.87, 118.79, 118.89, 127.70, 129.74, 129.77, 133.03, 133.10, 133.28, 135.24, 135.49, 135.53, 135.61, 136.29, 136.47. Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79. Found: C, 72.33; H, 8.82.

(2*R*,3*R*,4*R*,5*R*/*S*,6*R*/*S*,7*S*,8*R*)-1,2:7,8-Di-*O*-isopropylidene-4-methyl-5-vinyldecane-1,2,3,6,7,8-hexol (68). Allylic bromide **27** (3.57 g, 9.67 mmol) and **67a** (1.53 g, 9.67 mmol) were treated with a suspension of $CrCl_3$ (4.13 g, 26.1 mmol) and $LiAlH_4$ (0.50 g, 13.2 mmol) in THF (120 mL) to provide after column chromatography (hexane/ethyl acetate (3:1)) **68** (1.72 g, 40%) in a diastereomeric mixture of 2.5:1. The diastereomers were separated by HPLC (0.5% 2-propanol in hexane). Major diastereomer: colorless oil; $[\alpha]^{20}_D$ +38.7 (c 0.67); IR (film) ν_{max} 3460, 3070, 3040, 2985, 2940, 2880, 1455, 1380, 1370, 1245, 1220, 1160, 1060, 1000, 995, 970, 950, 920, 875, 860, 735, 700, 515 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3 H, J = 7.5 Hz, H-10), 1.08 (d, 3 H, J = 7.5 Hz, CH_3), 1.26, 1.36, 1.43 (each s, 12 H, acetonides), 1.50 (mc, 2 H, H-9), 1.89 (m, 1 H, H-4), 2.58 (m, 1 H, H-5), 3.40 (dd, 1 H, J = 7, 4.5 Hz, H-3), 3.43 (s, 1 H, OH), 3.56 (t, 1 H, J = 8, 8 Hz, H-1), 3.45–4.08 (m, 4 H, H-1′, 6, 7, 8), 4.39 (ddd, 1 H, J = 8, 8, 7 Hz, H-2), AB system (δ_A = 4.60, δ_B = 4.94, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 4.94 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.19 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.99 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.33 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.60, 17.57, 22.71, 25.51, 25.78, 26.66, 28.38, 39.06, 48.96, 66.55, 67.30, 74.75, 77.50, 78.84, 79.80, 84.42, 107.34, 109.08, 118.54, 127.65, 127.93, 128.23, 136.84, 138.08; MS (EI, 160 eV, 130 °C), m/e 101 (20.52), 91 (100, [C_7H_7]$^+$), 59 (32.65), 43 (40.07). Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.27; H, 9.03.

Minor diastereomer: colorless oil; $[\alpha]^{20}_D$ +7.2 (c 0.66, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, 3 H, J = 7 Hz, H-10), 1.15 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.34, 1.36, 1.41, 1.44 (each s, each 3 H, acetonides), 1.50 (mc, 2 H, H-9), 2.00–2.25 (m, 2 H, H-4, H-5), 2.30 (d, 1 H, J = 2.5 Hz, OH), 3.42 (dd, 1 H, J = 6, 3 Hz, H-3), 3.67 (t, 1 H, J = 8, 8 Hz, H-1), 3.92 (mc, 3 H, H-6, H-7, H-8), 4.01 (dd, 1 H, J = 8, 5 Hz, H-1), 4.30 (ddd, 1 H, J = 8, 6, 5 Hz, H-2), AB system (δ_A = 4.60, δ_B = 4.69, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 5.00 (dd, 1 H, J = 17, 2 Hz, vinylic-CH_2), 5.19 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.83 (ddd, 1 H, J = 17, 10, 10 Hz, vinylic-CH), 7.33 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.70, 14.74, 22.96, 25.86, 26.50, 28.23, 36.18, 48.04, 66.21, 68.41, 72.69, 77.26, 77.51, 78.35, 78.98, 81.46, 107.67, 108.95, 118.08, 127.33, 127.68, 128.14, 137.81, 138.87. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.69; H, 9.15.

Synthesis of Nephromopsinic Acid and Its Enantiomer. (2*R*,3*S*,4*S*,5*S*,6*S*)-3-*O*-Benzyl-4-methyl-5-vinylnonadecane-1,2,3,6-tetrol (70a). Deprotection of **38** (0.53 g, 1.05 mmol) with MeOH (50 mL) and p-TsOH was accomplished analogously to the procedure described above for **52b** to give after purification by column chromatography (hexane/ethyl acetate (1:1)) **70a** (0.41 g, 84%) as a colorless oil: $[\alpha]^{20}_D$ +1.4 (c 2.1, $CHCl_3$); IR (film) ν_{max} 3400, 2930, 2860, 1480–1190, 1150–980, 920, 735, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 7 Hz, H-19), 0.99 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.14–1.59 (m, 24 H, H-7-18), 2.08 (m, 1 H, H-4), 2.45 (ddd, 1 H, J = 10, 5, 5 Hz, H-5), 2.52 (m, 3 H, OH), 3.73 (mc, 5 H, H-1, 2, 3, 6), AB system (δ_A = 4.76, δ_B = 4.74, 2 H, J_{AB} = 11.5 Hz, benzyl-CH_2), 5.13 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.27 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.82 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.34 (mc, 5 H, aryl-H); ^{13}C NMR

(63 MHz, $CDCl_3$) δ 13.96, 14.19, 22.54–35.17, 50.66, 63.80, 72.35, 72.38, 73.92, 83.13. 118.45, 127.44, 128.23, 136.90, 138.42; MS (EI, 70 °C) *m/e* 463 (0.57), 402 (30.87), 401 (100), 383 (42.36), 365 (24.85), 293 (27.06), 91 (100, $[C_7H_7]^+$), 69 (22.85). Anal. Calcd for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.45; H, 10.95.

(2*R*,3*S*,4*S*,5*S*,6*S*)-4-Methyl-5-vinylnonadecane-1,2,3,6-tetrol (70b). Debenzylation of **70a** (2.1 g, 4.54 mmol) in THF/ammonia (100 mL, 1:1 mixture) with sodium chips, according to the procedure described for the preparation of **44**, furnished after column chromatography (ethyl acetate) **70b** (1.56 g, 92%) as a colorless oil: IR (film) ν_{max} 3350, 3070. 2920, 2840, 1460, 1415, 1375, 1325, 1050, 910, 885, 725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, 3 H, H-19), 0.95 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.17–1.61 (m, 24 H, H-7-18), 1.88 (m, 1 H, H-4), 2.09 (s, 1 H, OH), 2.34 (ddd, 1 H, J = 10, 5, 5 Hz, H-5), 2.38 (s, 1 H, OH), 3.00 (s, 2 H, OH), 3.73 (m, 5 H, H-1, 2, 3, 6), 5.18 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.27 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.87 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.15–13.74, 22.35–36.25, 51.69, 71.60, 75.92, 76.24, 76.75, 118.43, 136.52; MS (EI, 80 °C) *m/e* 325 (67.28), 323 (100), 311 (45.46), 111 (100), 69 (45.06). 68 (47.99). Anal. Calcd for $C_{22}H_{44}O_4$: C, 70.92; H, 11.90. Found: C, 70.73; H, 11.76.

(2*R*/*S*,3*S*,4*S*,5*S*)-3-Methyl-2-oxy-5-tridecyl-4-vinyltetrahydrofuran (71). To a stirred solution of tetrol **70b** (0.92 g, 2.47 mmol) in diethyl ether (100 mL), H_5IO_6 (1.14 g, 5.0 mmol) was added at 22 °C. After 1 h of stirring, the mixture was concentrated and diluted with methanol (100 mL), followed by addition of K_2CO_3 until the pH rose above 8. After stirring for an additional 15 min. the solvent was evaporated, and the residue was diluted with ether (70 mL) and water (20 mL). Extraction of the aqueous layer with ether and drying of the combined etheric phases ($MgSO_4$), followed by chromatography of the concentrated residue (hexane/ethyl acetate (5:1)), furnished **71** (0.56 g, 73%) as a white amorphous solid: IR (KBr) ν_{max} 3420, 3090, 2930, 2860, 1465, 1105, 995, 920, 725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (t, 6 H, J = 7 Hz, tridecyl-CH_3), 1.00 (d, 3 H, J = 7 Hz, C-3-CH_3), 1.08 (d, 3 H, J = 7 Hz, C-3-CH_3). 1.17–1.60 (m, 48 H, tridecyl-CH_2), 2.00 (mc, 2 H, H-3), 2.48 (m, 1 H, H-4), 2.69 (m, 1 H, H-4), 2.96 (d, 1 H, J = 4 Hz, OH), 3.41 (d, 1 H, J = 5 Hz, OH), 4.08 (m, 1 H, H-5), 4.28 (m, 1 H, H-5), 5.10 (mc, 4 H, vinylic-CH_2), 5.36 (mc, 2 H, H-2), 5.76 (mc, 2 H, vinylic-CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.37, 14.05, 15.34, 20.87–32.60, 43.10, 45.81, 51.13, 54.35, 80.83, 81.68, 98.85, 104.83, 116.63, 117.28, 136.60, 136.68; MS (EI, 40 °C) *m/e* 310 (0.52, $[M]^+$), 109 (44.89), 98 (95.12), 69 (50.25), 42.9 (100). Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33. Found: C, 77.53; H, 12.65.

(3*S*,4*S*,5*S*)-3-Methyl-2-oxo-5-tridecyl-4-vinyltetrahydrofuran (72). **71** (0.44 g, 1.42 mmol) in CH_2Cl_2 (5 mL) was added to a stirred suspension of PCC (pyridinium chlorochromate) (1.54 g, 7.14 mmol, 5 equiv) in CH_2Cl_2 (200 mL) at 0 °C. After stirring for 2 h at 22 °C, ether (200 mL) and $MgSO_4$ (2 g, 17 mmol) were added. Filtration, evaporation of volatiles and purification of the residue by column chromatography (hexane/ethyl acetate (5:1)) furnished **72** (0.40 g, 92%) as colorless crystals: mp 28 °C; $[\alpha]^{20}_D$ −66.6 (*c* 1.04, $CHCl_3$); IR (KBr) ν_{max} 2930, 2860, 1775 (lactone-C=O), 1470, 1460, 1380, 1355, 1320, 1175, 1140, 1000, 975, 925 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, tridecyl-CH_3), 1.22 (d, 3 H, J = 7 Hz, C-3-CH_3), 1.24 (s, 22 H, C-2′-C-12′-tridecyl-CH_2), 1.51 (m, 2 H, C-1′-tridecyl-CH_2), 2.49 (dq, 1 H, J = 11, 7 Hz, H-3), 2.81 (ddd, 1 H, J = 11, 9, 8 Hz, H-4), 4.48 (m, 1 H, J = 8 Hz, H-5), 5.22 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.25 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.73 (ddd, 1 H, J = 17.5, 10, 9 Hz, vinylic-CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.48, 14.05, 22.64–31.89, 38.46, 51.46, 80.92, 118.84, 133.96, 178.68; MS (EI, 40 °C) *m/e* 308 (1.15, $[M]^+$), 68 (100). Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 77.93; H, 11.58.

(3*S*,4*S*,5*S*)-4-Carboxy-3-methyl-2-oxo-5-tridecyltetrahydrofuran (Nephromopsinic Acid) ((−)-69). To a stirred solution of lactone **72** (155 mg, 0.50 mmol) in a solvent mixture of CCl_4 (1 mL), CH_3CN (1 mL), and water (1.5 mL) were added $NaIO_4$ (439 mg, 2.05 mmol) and ruthenium(III) chloride (10 mg, 0.05 mmol) at 22 °C. After 2 h at ambient temperature, CH_2Cl_2 (2 mL) was added, and the aqueous phase was separated and extracted with CH_2Cl_2. The combined organic layers were filtrated over a pad of Celite. After evaporation of volatiles, the residue was diluted with ether (2 mL) and saturated aqueous $NaHCO_3$ solution (2 mL). The etheric phase was separated, and the aqueous one was acidified with hydrochloric acid (3 mL, 7%). The precipitate was separated by filtration, washed with water (1 mL, 0 °C), and gave (−)-**69** (100 mg, 62%) as white crystals, which could be purified by dissolving them in ethanol and dilution with water: mp 136 °C (lit.[24] mp 137 °C); $[\alpha]^{20}_D$ −84 (*c* 0.25, $CHCl_3$) (lit.[24] $[\alpha]^{20}_D$ −85.1); IR (KBr) ν_{max} 3450 (carboxyl-OH), 3030, 2980, 2950, 2910, 2840, 1740 (lactone-C=O), 1465, 1415, 1355, 1330, 1245 (OH), 1200 (C—O), 1180 (C—O), 1010, 980, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, tridecyl-CH_3), 1.29 (m, 22 H, [C-2′-C-22′]-tridecyl-CH_2), 1.38 (d, 3 H, J = 7 Hz, CH_3), 1.58 (m, 2 H, C-1′-tridecyl-CH_2), 3.04 (dq, 1 H, J = 10, 7 Hz, H-3), 3.22 (dd, 1 H, J = 10, 8.5 Hz, H-4), 4.70 (m, 1 H, H-5), 5.50 (s, br 1 H, carboxyl-OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.02, 14.39, 22.62–31.86, 36.44, 51.56, 77.31, 175.00, 177.34 (carboxyl-C); MS (EI, 120 °C) *m/e* 326 (6.01, $[M]^+$) 117.0 (40.19), 99 (26.34), 56 (32.72), 55 (83.82). 44 (53.6), 43 (100), 40.8 (80.69). Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.97; H, 10.71.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3-*O*-Benzyl-4-methyl-5-vinylnonadecane-1,2,3,6-tetrol (73a). Deprotection of **40** (0.53 g, 1.05 mmol) with MeOH (50 mL) and *p*-TsOH as described furnished after column chromatography (hexane/ethyl acetate (1:1)) **73a** (0.4 g, 85%) as a white amorphous solid: IR and MS data see **70a**; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 7 Hz, H-19), 0.97 (d, 3 H, J = 7 Hz, C-4-CH_3), 1.16–1.60 (m, 24 H, H-7-18), 1.68 (d, 1 H, J = 4 Hz, OH), 2.20 (m, 1 H, H-4), 2.28 (s, 1 H, OH), 2.28 (ddd, 1 H, J = 10, 5, 5 Hz, H-5), 2.54 (d, 1 H, J = 8 Hz, OH), 3.40 (m, 1 H, H-3), 3.61 (mc, 3 H, H-1, 6), 3.78 (m, 1 H, H-2), AB system (δ_A = 4.53, δ_B = 4.75, 2 H, J_{AB} = 11 Hz, benzyl-CH_2), 5.14 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.29 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.80 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH), 7.33 (mc, 5 H, aryl-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.63, 14.04, 22.62, 25.47, 29.29, 29.62, 31.86, 34.82, 35.45, 50.84, 65.03, 71.47, 73.64, 80.71, 119.53, 127.61, 127.83, 128.44, 136.33, 137.94.

(2*R*,3*R*,4*R*,5*R*,6*R*)-4-Methyl-5-vinylnonadecane-1,2,3,6-tetrol (73b). According to the debenzylation of **70a**, benzyl ether **73a** (1.30 g, 2.81 mmol) in THF/ammonia (100 mL, 1:1 mixture) was deprotected by addition of sodium. Usual workup gave after column chromatography (ethyl acetate) **73b** (0.98 g, 94%) as a white amorphous solid: IR and MS data see **70b**; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (m, 6 H, C-4-CH_3 and H-19), 1.12–1.60 (m, 24 H, H-7-18), 1.99 (m, 1 H, H-4), 2.29 (ddd, 1 H, J = 10, 5, 5 Hz, H-5), 3.11 (d, 1 H, OH), 3.40 (m, 1 H, H-6), 3.71 (mc, 4 H, H-1, -2, -3), 4.04 (s, 1 H, OH), 4.10 (d, 1 H, J = 5 Hz, OH), 4.22 (s, 1 H, OH), 5.12 (dd, 1 H, J = 17.5, 2 Hz, vinylic-CH_2), 5.21 (dd, 1 H, J = 10, 2 Hz, vinylic-CH_2), 5.78 (ddd, 1 H, J = 17.5, 10, 10 Hz, vinylic-CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.38, 14.03, 22.63, 25.93, 29.31, 29.68, 31.88, 34.72, 36.75, 51.75, 65.81, 70.54, 71.94, 75.25, 118.96, 136.55. Anal. Calcd for $C_{22}H_{44}O_4$: C, 70.92; H, 11.90. Found: C, 71.31; 11.87. The synthesis of *ent*-**71**, *ent*-**72**, and *ent*-**69** was accomplished in accordance with the preparation described above for **71**, **72**, and (−)-**69**. The chromatographic (HPLC) and spectroscopic (^1H/^{13}C NMR, IR, MS) properties of these compounds were identical, respectively, and differed only in the sign of the optical rotation.

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Supplementary Material Available: Procedures and analytical data (^1H/^{13}C NMR, IR, MS spectra, optical rotations, combustion analysis) of compounds not described in the Experimental Section, NOE experiments for **43**, **55**, **58**, and **64**, and tables of atomic coordinates and bond angles and distances for **44** and **57** (48 pages); tables of observed and calculated crystal structure factors for **44** and **57** (26 pages). Ordering information is given on any current masthead page.