[(Z)-γ-[(Diisopropylidene-α-D-mannopyranosyl)oxy]allyl]-tributylstannane: A New Chiral Reagent for the Asymmetric α-Hydroxyallylation of Aldehydes

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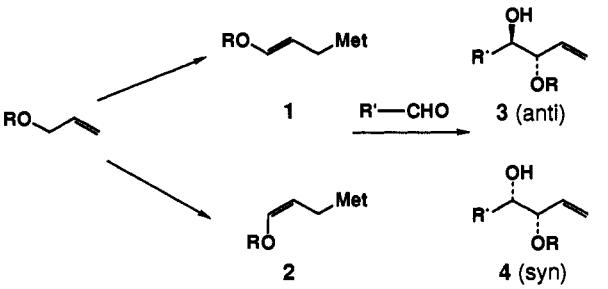
Abstract: Reactions of [(*Z*)-γ-[(diisopropylidene-α-D-mannopyranosyl)oxy]allyl]tributylstannane (**6**) with several chiral and achiral aldehydes are described. This reagent was designed in anticipation that significant diastereofacial bias in reactions with aldehydes would be exerted by the mannosyl auxiliary as a consequence of the exo anomeric effect. In fact, chiral reagent **6** displays especially useful diastereoselectivity in $BF_3 \cdot OEt_2$-promoted matched double asymmetric reactions with chiral aldehydes (*S*)-**7** (18:1 selectivity), (*R*)-**19** (≥20:1 selectivity), and (*R*)-**26** (≥20:1 selectivity). Reagent **6** also gives good to excellent selectivity in mismatched double asymmetric reactions with (*R*)-**7** (16:1 selectivity), (*S*)-**19** (5:1 selectivity), (*S*)-**20** (7:1 selectivity), but with (*S*)-**26** the mismatched double diastereoselectivity falls to 2:1. Reagent **6** also participates in $MgBr_2$-promoted reactions with α-alkoxy aldehydes (e.g., **19**), although it proved incapable of overriding the intrinsic diastereofacial bias of the $MgBr_2$-complexed aldehyde. In all cases, it appears that the aldehyde–Lewis acid complexes approach the allylstannane unit of **6** on the side opposite to the pyran C–O bond with the vinyl ether C–O bond oriented anti to the pyranoside C(1)–C(2) bond, as dictated by the exo anomeric effect. However, reactions of **6** with α-(benzyloxy)acetaldehyde (**45**) demonstrate that the enantioselectivity of the reagent is attenuated by the tendency of reactions to occur via transition states with the enol ether either in the s-trans (e.g., **53**, **56**) or the less stable s-cis rotamer (e.g., **54**, **57**), which exhibit opposite enantiofacial selectivities. It is suggested that double asymmetric reactions involving **6** display synthetically useful levels of enantioselectivity because the chiral aldehydes are able to discriminate between the s-cis/s-trans rotamer pool such that the matched pair double asymmetric reactions proceed almost exclusively via transition states with s-trans enol ether rotamers. Pathways involving s-cis enol ether rotamers (cf., **32**, **43**) become significant in mismatched double asymmetric reactions of aldehydes with very large intrinsic diastereofacial preferences, as in the reactions of **6** with (*S*)-**26**-$BF_3 \cdot Et_2O$ and (*R*)-**19**-$MgBr_2$.

The stereoselective synthesis of carbohydrates and other polyoxygenated materials from acyclic precursors is a problem of considerable interest.[2] Procedures that enable syn or anti 1,2-diol units to be generated in concert with a C–C bond-forming event are particularly attractive, especially if the method is highly stereoselective. Among several different strategies that have been described, the α-alkoxyallylation of aldehydes via reactions with (γ-alkoxyallyl)metal reagents has received considerable attention.[3-5] Particularly noteworthy are the contributions of Brown,[5b] Marshall,[5c,d] and Yamamoto[5e] who have developed highly enantioselective procedures for the synthesis of syn diol monoethers **4** via the reactions of aldehydes with chiral ((*Z*)-γ-alkoxyallyl)-boranes and ((*Z*)-γ-alkoxyallyl)stannanes, respectively. We,[6a,b] and subsequently Barrett,[6c] developed a procedure for the enantioselective synthesis of anti-1,2-diols **3** (R = H) via the reactions of aldehydes with chiral (*E*)-γ-(alkoxydimethylsilyl)oxy)-allylboron reagents, the silyl group serving as a hydroxyl surrogate.[7]



We report herein an alternative strategy for the stereoselective synthesis of syn 1,2-diol monoethers **4** via the reactions of chiral aldehydes and the new allylstannane reagent **6** that incorporates a mannosyl unit as a chiral auxiliary.[8] This reagent is easily prepared from allyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside **5**[9] by metalation with n-BuLi in THF–HMPA at −78 °C followed by treating the allyl anion with Bu_3SnCl (95%

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(1) (a) Taken in part from the 1992 Ph.D. Thesis of M.S.V., Indiana University. (b) Recipient of the 1991–92 Amoco Fellowship at Indiana University.

(2) (a) *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; ACS Symposium Series 386; Washington, DC, 1989. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (c) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. (d) Zamojski, A.; Banaszek, A.; Grynkiewicz, C. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 400.

(3) Reviews of reactions of allylorganometallics and aldehydes, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(4) γ-Alkoxyallylboron reagents: (a) Hoffmann, R. W.; Kemper. B. *Tetrahedron Lett.* **1980**, 4883. (b) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982**, *47*, 2498. (c) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246. (d) Roush, W. R.; Lesur, B. M.; Harris, D. J. *Tetrahedron Lett.* **1983**, *24*, 2227. Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (e) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353. (f) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881. (g) (γ-Alkoxyallyl)aluminum reagents: Koreeda, M.; Tanaka, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 845. (h) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1982**, 237. (i) γ-Alkoxyallyltin reagents: Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (j) Koreeda, M.; Tanaka, Y. *Ibid.* **1987**, *28*, 143. (k) Other methods involving allylmetal reagents: Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 1279; **1981**, 1005. (l) Yamamoto, Y.; Saito, S.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311. (m) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957. (n) Yamada, J.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118.

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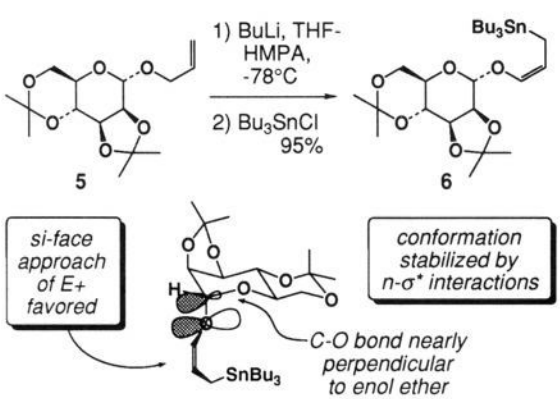
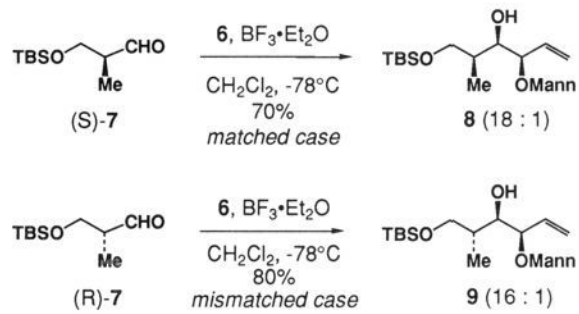
yield).[4i,j] While our studies were in progress, a chiral, carbohydrate-derived [γ-(tetrahydropyranyloxy)allyl]stannane, with the allylstannane linked to the auxiliary via C(2) rather than C(1) as in **6**, was reported by Yamamoto and co-workers.[5e]

Design Criteria. Chiral reagent **6** was designed in anticipation that significant diastereofacial bias would be exerted by the mannosyl auxiliary as a consequence of the exo anomeric effect.[10] This effect, which provides a basis for rationalization of the conformational preference of glycosidic bonds, has been attributed to the minimization of nonbonded interactions and the overlap of a nonbonding lone pair of electrons on the aglycon oxygen and the pyran σ^* C–O bond. However, C-disaccharides preferentially adopt similar conformations, suggesting that the conformational preferences of glycosides may be largely steric rather than stereoelectronic in nature.[11] For glycosides with sp^3-hybridized ether linkages, the preferred conformation about the glycosidic bond is almost always one in which the aglycon C(1′)–O(1) bond is antiperiplanar to the pyran C(1)–C(2) bond, and consequently the aglycon C–O bond is synclinal to the anomeric H and the pyran oxygen. Data summarized by Deslongchamps indicates that the anti C(1′)–O(1)–C(1)–C(2) conformation of an axial glycoside is stabilized by up to 1.9 kcal mol^{-1} relative to the next best conformation.[10a] For glycosides like **6** with sp^2-hybridized vinyl ether linkages,[12ab] the pyran C–O bond is expected to be essentially perpendicular to the plane of the enol ether unit.



Assuming that a conformation resembling the one depicted for **6** is adopted in the transition state for reactions with aldehydes, it follows that a Lewis acid complexed aldehyde should approach the *si* face of the enol ether since the pyran–aglycon O–C(1)–C(2) unit is a rather flat, unhindered surface (as long as the auxiliary has the C(2)-manno configuration). Approach of the electrophile to the opposite (*re*) face is expected to lead to the development of significant nonbonded interactions between the electrophile and the pyran C–O unit. Finally, it should be noted that the exo-anomeric effect has previously been invoked to explain the diastereoselectivity of Diels–Alder reactions of (*E*)-3-[(trimethylsilyl)oxy]buta-1,3-dienyl-β-glucopyranoside.[12a] Several other stereoselective reactions of glycosyl vinyl ethers can be interpreted similarly.[8,12]

BF_3·Et_2O-Catalyzed Double Asymmetric Reactions with β-Alkoxy-α-methylpropionaldehyde 7. Double asymmetric reactions of **6** with both enantiomers of β-alkoxy-α-methylpropionaldehyde **7** were examined as an initial test of this strategy.[13] Thus, the reaction of **6** (1.5 equiv) and (*S*)-**7** in CH_2Cl_2 at −78 °C in the presence of BF_3·OEt_2 (typically 2–4 equiv) provided **8** as the major product of an 18:1 mixture. In contrast, the reaction of **6** and the enantiomeric chiral aldehyde (*R*)-**7** proceeded with completely reversed diastereoselectivity and provided **9** as the major component of a 16:1 mixture. Keck has previously shown that the BF_3·Et_2O-catalyzed reactions of **7** with (*E*)- or (*Z*)-crotylstannanes generally favor the all syn diastereomer corresponding to **8**.[14] Therefore, we conclude that the enantioselectivity of chiral allylstannane **6** is sufficient to completely overcome the intrinsic diastereofacial bias of (*R*)-**7** in the mismatched double asymmetric reaction that provides **9** as the major product.



The stereostructures of **8** and **9** were assigned following conversion to triacetates **10** and **11**. A reference sample of **11** was prepared via the chelate-controlled reaction of (*R*)-**12** and (γ-alkoxyallyl)stannane **13**[4i] followed by standard functional group manipulations of the product **14** ((i) Na, NH_3; (ii) TBAF, THF; (iii) Ac_2O, pyridine)). Reference samples of triacetates **15** and **16** were prepared from the corresponding triol mono-TBS ethers deriving from our earlier studies.[6a,b] Triacetate **10** deriving from **8** is a diastereomer of **11**, **15**, and **16** and, therefore, is the fourth isomer in this series.

The stereochemical outcome of the matched double asymmetric reaction of **6** and (*S*)-**7** can be rationalized by invoking either transition state $\mathbf{17}_{\text{synclinal}}$ or $\mathbf{17}_{\text{anti}}$. In both cases the aldehyde approaches the *si* face of the allylstannane and adopts the usually preferred Felkin rotamer with the methyl group eclipsing the carbonyl and the $TBSOCH_2$– group positioned anti to the developing C–C bond.[15] It is also assumed that the BF_3–aldehyde

(5) Chiral (γ-alkoxyallyl)metal reagents useful for the enantioselective synthesis of syn diols: (a) Wuts, P. G. M.; Bigelow, S. S. *J. Chem. Soc., Chem. Commun.* **1984**, 736. (b) Brown, H. C.; Jadhav, K. P.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (c) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 2183. (d) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1991**, *56*, 483. (e) Yamamoto, Y.; Kobayashi, K.; Okano, H.; Kadota, I. *Ibid.* **1992**, *57*, 7003.

(6) (a) Roush, W. R.; Grover, P. T.; Lin, X.-F. *Tetrahedron Lett.* **1990**, *31*, 7563. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981. (c) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243.

(7) For a highly enantioselective synthesis of anti-glycolates via the aldol reaction: Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 1019.

(8) Review of carbohydrates as chiral auxiliaries: Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336.

(9) Gigg, R.; Payne, S.; Conant, R. *Carbohydr. Res.* **1985**, *141*, 9.

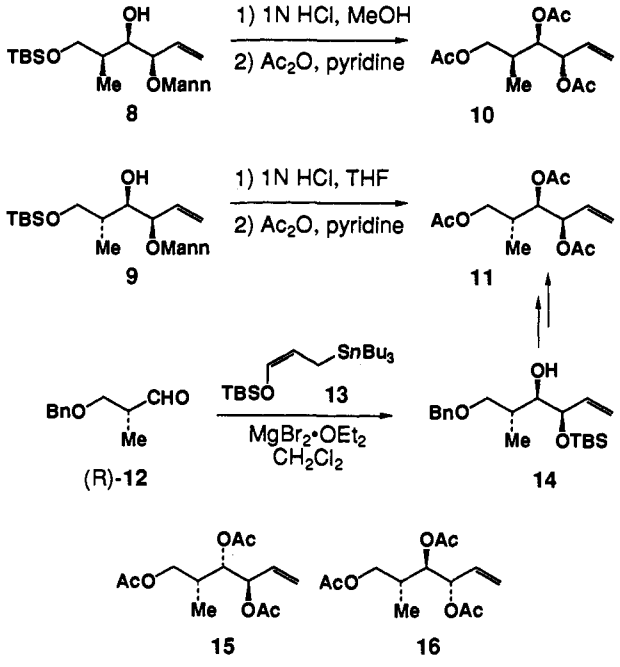
(10) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 4–29. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (c) Lemieux, R. L. *Pure Appl. Chem.* **1971**, *25*, 527.

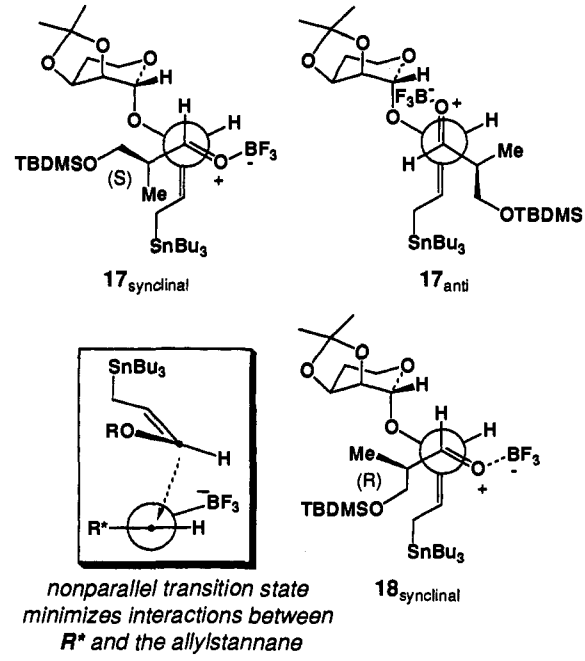
(11) (a) Goekjian, P. G.; Wu, T.-C.; Kishi, Y. *J. Org. Chem.* **1991**, *56*, 6412. (b) Wang, Y.; Goekjian, P. G.; Rychman, D. M.; Miller, W. H.; Babirad, S. A.; Kishi, Y. *Ibid.* **1992**, *57*, 482. (c) Haneda, T.; Goekjian, P. G.; Kim, S. H.; Kishi, Y. *Ibid.* **1992**, *57*, 490.

(12) (a) Gupta, R. C.; Slawin, A. M. Z.; Stoodley, R. J.; Williams, D. J. *Chem. Commun.* **1986**, 1116. (b) Gupta, R. C.; Larsen, D. S.; Stoodley, R. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 739. (c) Larsen, D. S.; Stoodley, R. J. *Ibid.* **1989**, 1841. (d) Edwards, W. D.; Gupta, R. C.; Raynor, C. M.; Stoodley, R. J. *Ibid.* **1991**, 1913. (e) Other studies involving glycosylated dienyl and enol ethers: David, S.; Lubineau, A.; Vatele, J.-M. *J. Chem. Soc., Chem. Commun.* **1975**, 701. (f) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1795 and references cited therein. (g) Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001. (h) Lubineau, A.; Auge, J.; Bellanger, N.; Caillebourdin, S. *Tetrahedron Lett.* **1990**, *31*, 4147. (i) Choudhury, A.; Franck, R. W.; Gupta, R. B. *Ibid.* **1989**, *30*, 4921. (j) Llera, J. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 2997. (k) Borer, B. C.; Balogh, D. W. *Tetrahedron Lett.* **1991**, *32*, 1039. (l) The chemistry reported in ref 5a has been reinterpreted in terms of the exo anomeric effect (see ref 3c). The diastereoselectivity relative to the THP substituent in the following paper may also be related: Metternich, R.; Hoffmann, R. W. *Tetrahedron Lett.* **1984**, *25*, 4095.

(13) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(14) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.





nonparallel transition state minimizes interactions between R and the allylstannane*

complex has the trans geometry.[16] Although anti relationships between the allylstannane and Lewis acid complexed aldehyde are often invoked in reactions of this type,[2bd,17] evidence has been presented that suggests that synclinal transition states (e.g., $\mathbf{17}_{\text{synclinal}}$) may be favored in some instances.[18,19] Assuming that the aldehyde and allylstannane π systems occupy nonparallel planes in the transition state,[3c,20] then $\mathbf{17}_{\text{synclinal}}$ should be the lowest energy transition structure since interactions between the mannosyloxy auxiliary and the substituents on the chiral aldehyde are minimized.

By similar arguments we conclude that transition state $\mathbf{18}_{\text{synclinal}}$ accounts for the formation of **9** as the major product of the mismatched double asymmetric reaction of **6** and (*R*)-**7**. The aldehyde adopts an "anti-Felkin" rotamer in this transition structure, with the larger $TBSOCH_2$– group eclipsing the carbonyl. Presumably the chiral reagent **6** is able to dominate the outcome of this reaction since the intrinsic diastereofacial selectivity of **7** is not overwhelmingly large.[14]

Double Asymmetric Reactions of 6 and α-Alkoxy Aldehydes 19 and 26. We explored the double asymmetric reactions of **6** with two additional chiral aldehydes in order to probe the limits of the enantioselectivity of the new chiral reagent **6**. The BF_3·Et_2O-promoted matched double asymmetric reactions of **6** with chiral α-alkoxy aldehydes (*R*)-**19**[21] and (*R*)-**26**[5d] provided **21** and **27** as the only observed diastereomers, presumably via synclinal transition state **30** (an anti transition state analogous to $\mathbf{17}_{\text{anti}}$ is also possible, vide supra). As in the previously described series of reactions with **7**, the diastereoselectivity is reversed in the mismatched double asymmetric reactions involving (*S*)-**19** and (*S*)-**26**. The reaction of **6** and (*S*)-**19** provided the all syn diastereomer **22** as the major component of a 5:1 mixture. Selectivity in the mismatched reaction was improved to 7:1 by using the TBS-protected lactaldehyde derivative (*S*)-**20**[21c] as the substrate.

The major products of the mismatched double asymmetric reactions of (*S*)-**19** and (*S*)-**20** presumably arise via synclinal transition state **31** (although an anti transition state cannot be ruled out rigorously, vide supra) in which the aldehyde adopts an anti-Felkin rotamer with the α-alkoxy group eclipsing the Lewis acid coordinated carbonyl group. These examples provide additional evidence of the enantioselectivity of the chiral reagent **6**, since α-alkoxy aldehyde·BF_3 complexes generally exhibit a significant preference to react with achiral allylstannanes by way of Felkin transition states.[22]

However, mismatched double diastereoselectivity was not as great in the BF_3·Et_2O-promoted reaction of **6** and (*S*)-**26**, which provided a 2:1 mixture of **28** and **29**. This result implies that the intrinsic diastereofacial preference of **26** is considerably greater than that of **7**, **19**, and **20**. The stereochemistry of the minor product **29** suggests that the reaction may proceed by way of transition state **32** in which the enol ether unit of **6** adopts the more hindered, less stable[23,24] s-cis conformation and the aldehyde reacts by way of the usually favored Felkin–Anh rotamer. Thus, in this case, the chiral reagent is only marginally capable of overriding the intrinsic diastereofacial preference of (*S*)-**19**. The energy cost for reaction by way of an anti-Felkin carbonyl rotamer (as in **31**) apparently is great enough to allow a competitive reaction to proceed by way of transition state **32** in which the aldehyde adopts the normal Felkin rotamer at the expense of the chiral enol ether unit of **6** that adopts an unfavorable conformation.

The stereostructures of **21**–**24** deriving from *O*-benzyllactaldehyde **19** were assigned as follows. Hydrolysis (1 N HCl, THF) of the all syn diastereomer **22** provided **33** which proved to be identical with a sample prepared via the chelate-controlled

(15) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(16) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

(17) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

(18) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, 64, 1413.

(19) (a) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970. (b) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655. (c) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Wilson, T. M. *Tetrahedron* **1989**, 45, 1053. (d) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1161. (e) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 3211. (f) Marshall, J. A.; Wang, X. *Ibid.* **1992**, *57*, 1242. (g) Gung, B. W.; Smith, D. T.; Wolf, M. A. *Tetrahedron* **1992**, *48*, 5455.

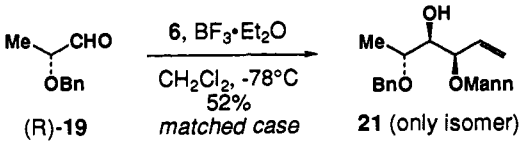
(20) Heathhcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

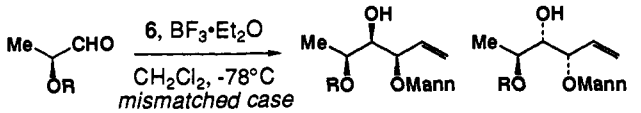
(21) (a) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768. (b) Mislow, K.; O'Brien, R. E.; Schaefer, H. *Ibid.* **1962**, *84*, 1940. (c) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1988**, *48*, 5180.

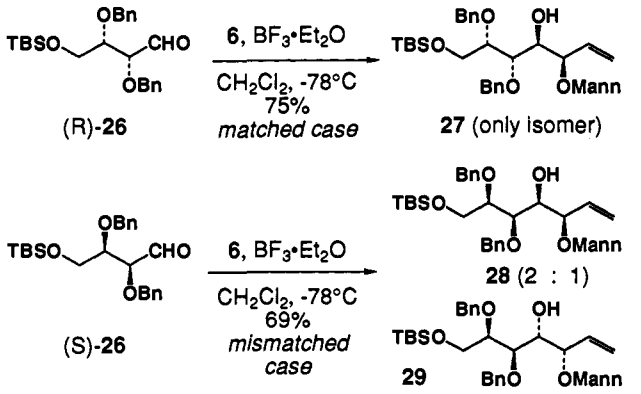
(22) BF_3·OEt_2-promoted additions of allylstannanes to α-(*tert*-butyldimethylsiloxy)-substituted aldehydes generally proceed with excellent Felkin–Anh diastereoselectivity (ref 14).

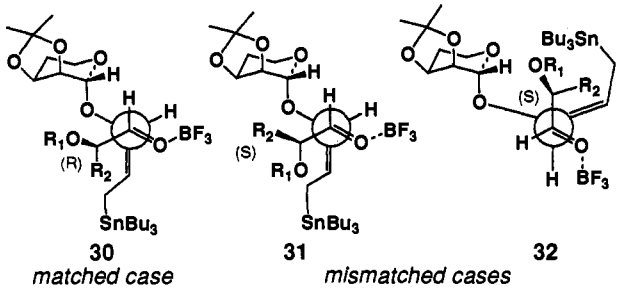
(23) (a) Charlton, J. L.; Plourde, G. L.; Penner, G. H. *Can. J. Chem.* **1989**, *67*, 1010. (b) Bond, D.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1003.

(24) For other diastereoselective transformations of chiral enol ethers: (a) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967 and references cited therein. (b) Prapansiri, V.; Thornton, E. R. *Tetrahedron Lett.* **1991**, *32*, 3147.





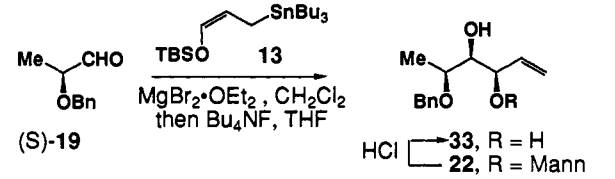


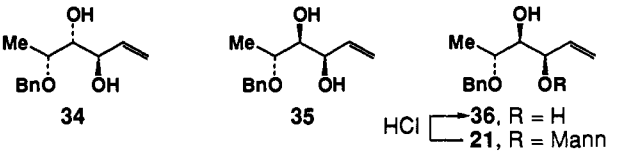


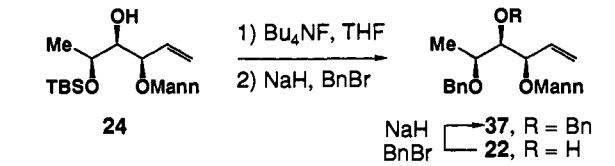
($MgBr_2$, CH_2Cl_2, –23 °C) reaction of (*S*)-**12** and (γ-alkoxyallyl)-stannane **13**[4i] followed by desilylation (Bu_4NF, THF). Reference samples of the 3,4-trans diastereomers **34** and **35** were available from previous studies in our laboratory.[6a,b] The stereostructure of **21** was established by hydrolysis to the fourth diastereomer in this series, namely **36**, the spectroscopic properties of which were clearly distinct from those of **33**–**35**. The stereostructure of **23**, the minor product of the mismatched double asymmetric reaction of (*S*)-**19** and **6**, was verified by hydrolysis to the enantiomer of **36**. Finally, the stereostructure of **24** was assigned by desilylation and benzylation which provided diether **37**, which proved identical to the benzylation product of **22**.

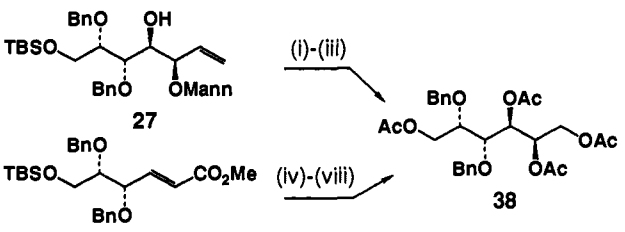
The stereochemistry of **27**, the sole product of the matched double asymmetric reaction of **6** and (*R*)-**26**, was assigned following conversion to tetraacetate **38** (i) O_3, MeOH–CH_2Cl_2, –78 °C, Me_2S; then $NaBH_4$; (ii) 0.5 N HCl, THF; (iii) Ac_2O, DMAP, pyridine). A reference sample of **38** was prepared by a sequence involving the diastereoselective (>10:1) osymlation of enoate **39** ((iv) OsO_4 (cat.), NMO; (v) TBSOTf, lutidine, CH_2Cl_2; (vi) DIBAL-H, Et_2O, –78 °C; (vii) TBAF, THF; (viii) Ac_2O, DMAP, pyridine).[25] This process is expected to provide the 3,4-anti stereochemical relationship in **38**.

Diastereomer **28**, the major product of the mismatched double asymmetric reaction of **6** and (*S*)-**26**, was assigned the all syn



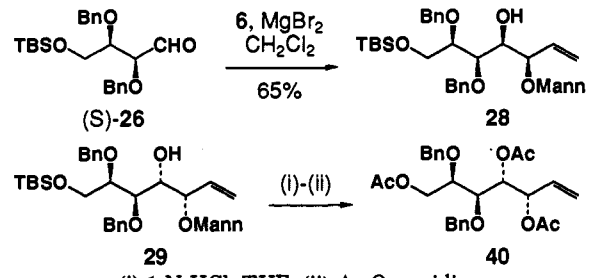






(i) O_3, MeOH–CH_2Cl_2, –78 °C; Me_2S; then $NaBH_4$; (ii) 0.5 N HCl, THF; (iii) Ac_2O, DMAP, pyridine; (IV) OsO_4 (cat.), NMO; (v) TBSOTf, lutidine, CH_2Cl_2; (vi) DIBAL-H, Et_2O, –78 °C; (vii) TBAF, THF; (viii) Ac_2O, OMAP, pyridine

stereochemistry since it was subsequently obtained as the near exclusive product of the $MgBr_2$·Et_2O-catalyzed reaction of **6** and (*S*)-**26** (vide infra). The identity of the minor diastereomer **29** was established by hydrolysis of the mannosyl auxiliary and TBDMS ether followed by peracetylation to give triacetate **40** ((i) 1 N HCl, THF; (ii) Ac_2O, pyridine), which proved to be the enantiomer of the triacetate similarly prepared from **27**.



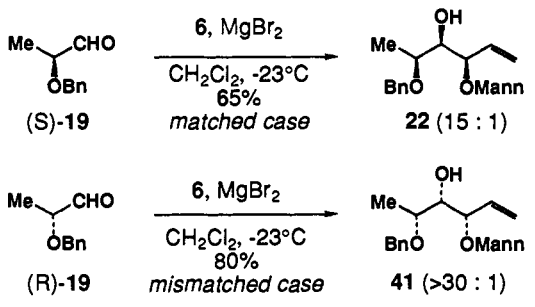
(i) 1 N HCl, THF; (ii) Ac_2O, pyridine

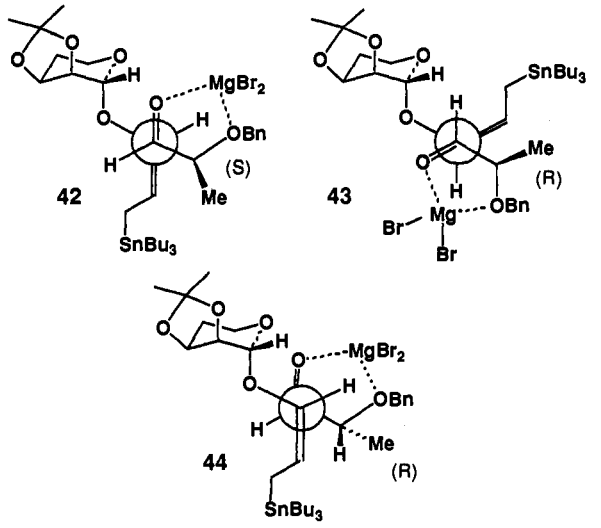
Chelate-Controlled Reactions of 6 and α-Alkoxy Aldehyde 19. While excellent results were obtained in the BF_3·Et_2O-promoted double asymmetric reactions of **6** and aldehydes (*S*)-**7** (matched), (*R*)-**7** (mismatched), (*R*)-**19** (matched), (*S*)-**19**/**20** (mismatched), and (*R*)-**26** (matched), the enantioselectivity of **6** was insufficient to achieve good selectivity in the mismatched double asymmetric reaction with (*S*)-**26**. Because the major product of this reaction, **28**, has the syn,syn stereochemistry that should be easily prepared by using chelate-controlled conditions,[4i,26] we decided to explore the reactions **6** with **19** and **26** in the presence of $MgBr_2$ in order to achieve more highly stereoselective access to **22** and **28**. As noted already in the preceding section, the reaction of **6** and (*S*)-**26** provided the all-syn diastereomer **28** with excellent selectivity.

(25) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, 24, 3943 and 3947. (b) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.

(26) Review of chelate-controlled carbonyl addition reactions: Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 556.

Results of the $MgBr_2$-catalyzed double asymmetric reaction of **6** with (*R*)-**19** and (*S*)-**19** are summarized below. Surprisingly, both reactions provided all syn diastereomers with excellent diastereoselectivity. Thus, the (presumably) matched double

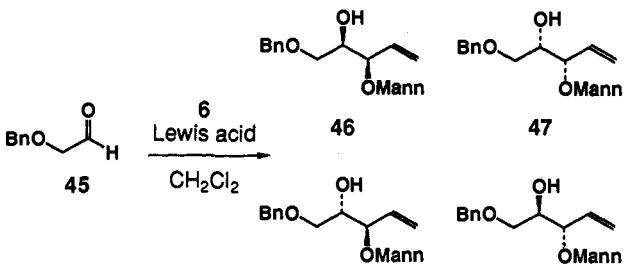




asymmetric reaction of **6** and (*S*)-**19** in the presence of $MgBr_2$ (CH_2Cl_2, –23 °C) provided **22** with 15:1 stereoselectivity, while the (presumably) mismatched $MgBr_2$-promoted reaction of **6** and (*R*)-**19** provided **41** with >30:1 selectivity. The stereochemistry of **41** was assigned by hydrolysis of the mannosyl auxiliary to give the enantiomer of syn,syn-diol **33**.

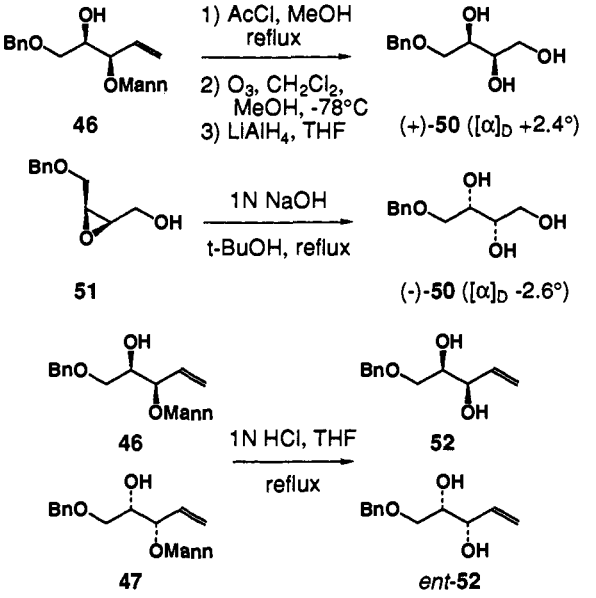
The reaction of (*R*)-**19** and **6** is expected to be a matched pair since the anti transition state **42** permits the allylstannane to adopt the usually preferred s-trans enol ether rotamer[23] and to approach the $MgBr_2$ chelated aldehyde from the less hindered face. An anti arrangement between the π systems of the two reactants should be favored in this instance since this permits the smallest substituent, H, of the allylstannane **6** to occupy a position over the five-membered chelate close to the sterically demanding $MgBr_2$ group. The results obtained in the mismatched double asymmetric reaction between (*R*)-**19** and **6** imply that the diastereofacial preference of the five-membered chelate is significantly greater than the enantioselectivity of the chiral reagent **6**. The stereochemistry of the major product, **41**, indicates that this reaction proceeds either by way of transition state **43** with the less stable s-cis enol ether rotamer or via transition structure **44** in which the Lewis acid complexed aldehyde approached the chiral allylstannane from the more hindered side, cis to the pyran C–O unit. We assume that **44** is less important than **43**, since the (*R*)-**19**·$MgBr_2$ complex is forced to approach the enol ether from the more hindered face, with the development of nonbonded interactions between the pyran and carbonyl oxygen atoms. That one or both of these transition structures are utilized establishes that the intrinsic diastereofacial preference of **6** (as indicated by the magnitude of the destabilizing interactions highlighted in **43**/**44**) is less than the diastereofacial preference of the **19**·$MgBr_2$ chelate (i.e., the preference of the nucleophile to add to the chelate on the side opposite the lactaldehyde methyl group).

BF_3·Et_2O-, $MgBr_2$-, and ZnI_2-Catalyzed Reactions of 6 with (Benzyloxy)acetaldehyde. Reactions with (benzyloxy)acetaldehyde (**45**) were performed in order to assess the intrinsic diastereofacial selectivity of **6** in the absence of the influence of stereogenic centers in the aldehyde component. Surprisingly, the results summarized below show that the BF_3·Et_2O-, $MgBr_2$-, and ZnI_2-catalyzed reactions are considerably less selective than the reactions of **6** with **7** or **19** under the same conditions. Because the stereoselectivity of these reactions was poor, efforts were not made to optimize the yields of isolated products.



Conditions	Yield	46	47	48,49
BF_3·Et_2O, -78°C	30%	7	1	1.5
$MgBr_2$, -23°C	56%	1.2	1	--
ZnI_2, 0°C	43%	1	1.5	0.2

The stereochemistry of **46** was assigned following hydrolysis of the mannosyl auxiliary and ozonolysis of the vinyl group. Triol (+)-**50** so prepared proved to be the enantiomer of (–)-**50** obtained by hydrolysis of epoxy alcohol **51**[27] via a base-catalyzed epoxide migration sequence.[27,28] Homoallyl alcohol **47** was similarly shown to be a syn diol by acidic hydrolysis of a 1.2:1 mixture of **46** and **47** (deriving from the $MgBr_2$-catalyzed reaction of **6** and **45**) that gave a single (essentially racemic) diol **52**.

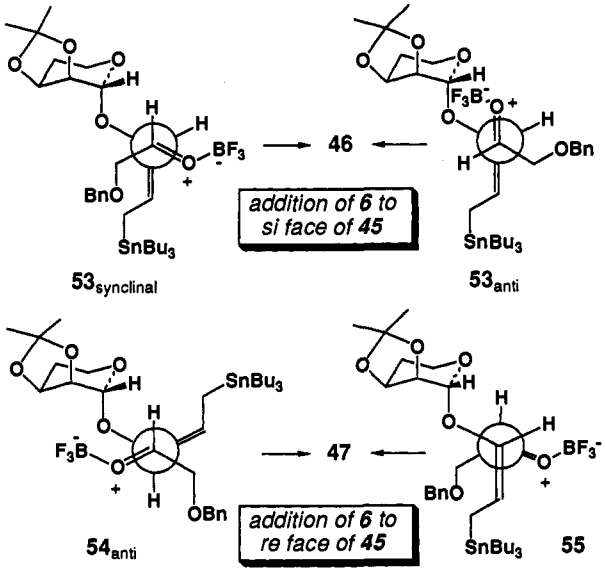


The stereochemistry of the major product **46** deriving from the BF_3·Et_2O-catalyzed reaction of **45** and **6** is consistent with a pathway involving transition structure $\mathbf{53}_{\text{synclinal}}$, by analogy to the reaction of **6** and (*S*)-**7** that proceeds via $\mathbf{17}_{\text{synclinal}}$. The minor syn diastereomer **47** probably arises via transition structure **54**,

(27) Katsuki, T.; Lee, A. W. M.; Ma, P.: Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.
(28) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

in which the enol ether unit of **6** adopts the less stable s-cis rotamer. Transition structure **55** is also a possible precursor to **47**, but we consider **55** to be less important than **54** owing to the fact that the Lewis acid complexed aldehyde approaches the allylstannane from the more hindered side.

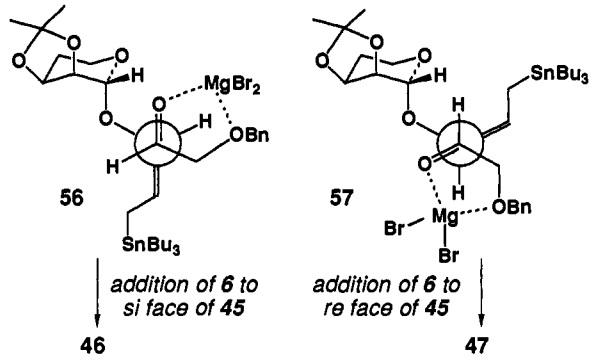
It is curious that the $BF_3{\cdot}Et_2O$-catalyzed reaction of **6** and (benzyloxy)acetaldehyde **45** is significantly less selective than the mismatched double asymmetric reaction of **6** and (*R*)-**7** and is comparable to the level of selectivity seen in the mismatched double asymmetric reactions of **6** and (*S*)-**19**/**20**, even though the diastereofacial selectivity preference of **19**/**20** is reasonably large.[22] Because the selectivity of the reaction of **6** with **45**–$BF_3{\cdot}Et_2O$ is only moderate (vide supra), application of Masamune's rule of multiplicativity to these reactions would suggest that the selectivity of the mismatched double asymmetric reactions should be poor.[13] That the mismatched reactions of **6** with **7** and **19**/**20** give good to excellent selectivity implies that the centers of chirality in the aldehyde substrates help to disfavor transition states (e.g., **54** and/or **55**) that contribute significantly in reactions with achiral aldehydes like **45**. That is, the chiral aldehydes seem able to select among a number of available transition states in such a way that the mismatched double asymmetric reactions are significantly more selective than should be possible based on the reactions of **6** with achiral substrates.



This point is demonstrated more dramatically in the $MgBr_2$- and $ZnCl_2$-catalyzed reactions of **45** and **6** which are virtually nonselective among the **46**/**47** syn diastereomer series. This indicates that the diastereomeric transition states **56** (leading to **46**) and **57** (leading to **47**) are virtually equivalent energetically.[29] Recall, however, that the reactions of **6** with **19** exhibit excellent diastereofacial selectivity. In this case, it is very clear that the stereocenter of **19** exhibits a significant effect on the reactions, since placement of an (*R*)-lactaldehyde stereoisomer in transition structure **42** (equivalent to **56**) or of (*S*)-lactaldehyde in **43** (equivalent to **57**) would force the allylstannane to approach the aldehyde from the more hindered face of the $MgBr_2$ chelate. Clearly, therefore, the chirality of **19** is sufficient to bias the s-cis/s-trans enol ether rotamer population in the competing reaction transition states.

Summary. We have demonstrated that the chiral (γ-alkoxyallyl)stannane **6** displays useful diastereoselectivity especially in $BF_3{\cdot}OEt_2$-promoted double asymmetric reactions with chiral aldehydes (*S*)-**7**, (*R*)-**19**, and (*R*)-**26**. The origin of asymmetry is believed to derive from conformational preferences of the (*Z*)-[(γ-mannosyl)oxy]vinyl ether dictated by the exo anomeric effect.

(29) A transition state analogous to **44** is also a potential precursor to **47**.



In all cases, it appears that the Lewis acid complexed aldehydes approach the allylstannane unit on the side opposite to the pyran C–O bond when the vinyl ether C–O bond is oriented anti to the pyranoside C(1)–C(2) bond. However, reactions of chiral reagent **6** with α-(benzyloxy)acetaldehyde (**45**) demonstrate that the enantioselectivity of **6** is attenuated by the tendency of reactions to occur via transition states with the enol ether in either the s-trans (e.g., **53**, **56**) or the less stable[23] s-cis rotamer (e.g., **54**, **57**), which have opposite enantiofacial selectivities. Evidently, double asymmetric reactions involving **6** exhibit synthetically useful levels of enantioselectivity because the chiral aldehydes are able to discriminate between the s-cis/s-trans rotamer pool such that the matched pair double asymmetric reactions proceed almost exclusively via transition states with s-trans enol ether rotamers. Pathways involving s-cis enol ether rotamers (cf., **32**, **43**) become significant only in the mismatched double asymmetric reactions of aldehydes with very large intrinsic diastereofacial preferences (e.g., reactions of **6** with (*S*)-**26**-$BF_3{\cdot}Et_2O$ and (*R*)-**19**-$MgBr_2$).

Experimental Section

General. All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether and THF were distilled from sodium benzophenone ketyl. Methylene chloride, toluene, and acetonitrile were distilled from CaH_2. Methanol was distilled from magnesium turnings.

^1H NMR spectra were measured at 300 MHz on a Varian XL-300 instrument at 400 MHz on a Varian VNMR 400 instrument and 500 MHz on a Bruker AM500 instrument. Residual chloroform (δ 7.26) was used as internal reference for spectra measured in $CDCl_3$. ^1H NMR spectra measured in C_6D_6 were referenced against residual benzene (δ 7.16). ^{13}C NMR spectra were recorded at 100.6 or 125.8 MHz and were referenced with the δ 77.0 resonance of $CDCl_3$ or the δ 128.0 resonance of C_6D_6. Infrared spectra were recorded on a Perkin-Elmer Model 1420 infrared spectrophotometer. FT-IR spectra were recorded on a Mattson Instruments 4020 Galaxy Series FT-IR spectrophotometer. Low- and high-resolution mass spectra were measured at 70 eV on a Kratos GC/MS 80 RFA mass spectrometer at the Indiana University Mass Spectrometry Laboratory. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1 mL capacity quartz cell with a 10 cm path length. Elemental analyses were performed by Robertson Laboratories, Florham Park, N. J. or Galbraith Laboratories, Knoxville, TN.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by staining (and charring) of the TLC plates with a solution of ceric sulfate and ammonium molybdate in aqueous sulfuric acid or with a solution of *o*-vanillin in ethanol with acetic and sulfuric acid. Flash chromatography was performed as described by Still using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh).[30] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^1H NMR analysis) for use in subsequent reactions.

(*Z*)-1-[(2,3:4,6-Di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]-3-(tributylstannyl)prop-1-ene (6). n-BuLi (2.6 M in hexanes, 8 mL, 20 mmol) was added dropwise to a vigorously stirred –78 °C solution of allyl ether **5**[9] (5 g, 16.6 mmol) in THF (30 mL). HMPA (3 mL) was added

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

immediately, and the resulting dark red solution was stirred at −78 °C for 30 min. Bu_3SnCl (4.95 mL, 18.3 mmol) was then added dropwise over 10 min.[4i] The resulting solution was stirred for 15 min and then allowed to warm slowly to room temperature. The reaction mixture was diluted with hexanes (120 mL) and poured into a vigorously stirred solution of saturated NH_4Cl (75 mL). The organic layer was separated, washed repeatedly with saturated LiCl (3 × 50 mL), and then dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give **6** (11.2 g, 95% yield) as a pale green oil that was sufficiently pure for use directly in reactions with aldehydes. Purification of large quantities of **6** was complicated by the acid lability of the enol ether. A small sample was purified by silica gel chromatography (1:1, Et_2O:hexanes) for characterization purposes: ^1H NMR (400 MHz, C_6D_6) δ 6.01 (d, J = 6.1 Hz, 1 H), 5.34 (s, 1 H), 4.77 (m, 1 H), 4.43 (dd, J = 5.9, 1.8 Hz, 1 H), 4.38 (d, J = 5.7 Hz, 1 H), 3.96 (m, 2 H), 3.86 (m, 1 H), 3.76 (dd, J = 10.0, 10.0 Hz, 1 H), 1.83 (m, 2 H), 1.64 (m, 6 H), 1.54 (s, 3 H), 1.46 (s, 3 H), 1.43 (m, 12 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 0.99 (t, 9 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 137.51, 109.45, 109.01, 99.69, 98.38, 76.17, 75.65, 73.18, 62.71, 62.38, 29.60, 29.60, 29.60, 29.33, 28.40, 27.78, 27.78, 27.78, 26.35, 18.70, 13.97, 13.97, 13.97, 9.73, 9.73, 9.73, 6.34; IR (neat) 2990, 2975, 2960, 2935, 1650, 1455, 1375, 1215, 1085, 1070, 860 cm^{-1}; LRMS m/e (relative intensity) 533 (24), 347 (19), 291 (100), 235 (53), 179 (32); HRMS for $C_{23}H_{41}O_6Sn$ [M^+ − Bu] calcd 533.1931, found 533.1925.

(2*S*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]-2-methylhex-5-en-3-ol (8). $BF_3{\cdot}Et_2O$ (171 μL, 1.4 mmol)[31] was added dropwise to a −78 °C solution of aldehyde (*S*)-**7** (94 mg, 0.46 mmol) in CH_2Cl_2 (3.5 mL). The resulting solution was stirred for 10 min, and then a solution of **6** (329 mg, 0.56 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise via cannula. The reaction mixture was stirred at −78 °C for 3.5 h, and then a solution of t-BuOK (465 mg, 4.1 mmol) in MeOH (4.0 mL) was added.[32] The mixture was allowed to warm to room temperature, diluted with EtOAc (30 mL), and washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (40% Et_2O in hexanes) afforded **8** (163 mg, 70% yield) as a clear oil as the major component of the 18:1 mixture: $[\alpha]^{25}_D$ = +28.7° (c = 1.8, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 5.61 (ddd, J = 17.2, 10.2, 8.1 Hz, 1 H), 5.51 (s, 1 H), 5.09 (ddd, J = 17.2, 1.6, 0.5 Hz, 1 H), 4.89 (dd, J = 10.4, 0.9 Hz, 1 H), 4.33 (A of ABX, J_{AB} = 6.5, J_{AX} = 7.5 Hz, 1 H), 4.25 (B of ABX, J_{AB} = 6.5 Hz, J_{BX} = 0.7 Hz, 1 H), 4.04–3.79 (complex set of overlapping signals, 5 H), 3.59 (A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 6.7 Hz, 1 H), 3.48 (B of ABX, J_{AB} = 9.7 Hz, J_{BX} = 5.1 Hz, 1 H), 2.58 (s, broad, 1 H), 1.66 (m, 1 H), 1.51 (s, 3 H), 1.47 (s, 3 H), 1.31 (s, 3 H), 1.21 (s, 3 H), 0.92 (s, 9 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.02 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 136.47, 117.80, 109.25, 100.02, 99.67, 83.28, 76.70, 75.71, 74.49, 73.38, 67.18, 62.29, 62.07, 36.54, 29.46, 28.47, 26.42, 26.07, 26.07, 26.07, 18.76, 18.43, 9.63, −5.36, −5.40; IR ($CHCl_3$) 3589, 3482 (broad), 3010, 2955, 2931, 2858, 1472, 1384, 1245, 1220, 1072, 934, 839; LRMS m/e (relative intensity) 271 (22), 243 (88), 201 (25), 185 (100), 143 (21), 127 (33), 111 (38), 85 (45), 69 (37); HRMS for $C_{25}H_{47}O_8Si$ [M + H^+] calcd 503.3040, found 503.3067.

(2*R*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]-2-methylhex-5-en-3-ol (9). $BF_3{\cdot}Et_2O$ (123 μL, 1.0 mmol)[31] was added dropwise to a −78 °C solution of (*R*)-**7** (50 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL). The resulting mixture was stirred for 10 min, and then a solution of **6** (295 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise via cannula. The resulting solution was stirred at −78 °C for 12 h, and then a solution of t-BuOK (337 mg, 3.0 mmol) in MeOH (2.0 mL) was added.[32] The solution was allowed to warm to room temperature, diluted with EtOAc (30 mL), and washed with H_2O (3 × 10 mL). The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel chromatography (19:1, CH_2Cl_2:acetone) provided alcohol **9** (101 mg, 80% yield) as a clear oil as the major component of the 16:1 diastereomeric mixture: $[\alpha]^{25}_D$ = +15.4° (c = 0.7, CHC_3); ^1H NMR (400 MHz, C_6D_6) δ 5.88 (ddd, J = 17.5, 10.4, 7.2 Hz, 1 H), 5.51 (s, 1 H), 5.21 (ddd, J = 17.5, 1.9, 1.1 Hz, 1 H), 4.97 (ddd, J = 10.4, 1.9, 0.8 Hz, 1 H), 4.37 (A of ABX, J_{AB} = 7.8 Hz, J_{AX} = 6.1 Hz, 1 H), 4.29 (B of ABX + overlapping t, 2 H), 4.04–3.84 (complex set of overlapping signals, 3 H), 3.76 (B of ABX, J_{AB} = 10.0 Hz, J_{BX} = 10.0 Hz, 1 H), 3.59 (d, J = 5.4 Hz, 2 H), 3.46 (dd, 1 H), 2.82 (d, J = 5.1 Hz, 1 H), 1.81 (m, 1 H), 1.52 (s, 3 H), 1.48 (s, 3 H), 1.31 (s, 3 H), 1.22 (s, 3 H), 0.91 (s, 9 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.06 (s, 6 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 137.10, 117.10, 109.27, 99.66, 99.64, 81.88, 78.02, 76.77, 75.75, 73.36, 65.74, 62.41, 62.08, 36.69, 29.42, 28.44, 26.37, 26.00, 26.00, 26.00, 18.70, 18.32, 14.97, −5.52, −5.52; IR ($CHCl_3$) 3451 (broad), 2995, 2956, 2930, 2858, 1731, 1463, 1404, 1246, 1081, 933, 838 cm^{-1}; LRMS m/e (relative intensity) 271 (27), 243 (78), 203 (55), 185 (100), 143 (20), 127 (34), 99 (21), 89 (48), 69 (34); HRMS for $C_{25}H_{47}O_8Si$ [M + H^+] calcd 503.3040, found 503.3046.

(2*R*,3*R*,4*R*)-2-(Benzyloxy)-4-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]-5-hexen-3-ol (21). $BF_3{\cdot}Et_2O$ (38 μL, 0.31 mmol)[31] was added dropwise to a −78 °C solution of aldehyde (*R*)-**19** (100 mg, 0.61 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine[33] (14 mg, 0.07 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 10 min, then a solution of **6** (383 mg, 0.65 mmol) in CH_2Cl_2 (1 mL) was added via cannula. The resulting solution was stirred at −78 °C for 3 h. The mixture was then poured into a vigorously stirred solution of saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (4 × 15 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (9:1, $CHCl_3$:acetone) to give **21** (141 mg, 52% yield) as a clear oil; no other diastereomers were detected by ^1H NMR analysis: $[\alpha]^{25}_D$ = +7.7° (c = 1.5, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 7.19 (m, 5 H), 5.79 (m, 1 H), 5.55 (s, 1 H), 5.10 (d, J = 16.1 Hz, 1 H), 4.91 (d, J = 10.5 Hz, 1 H), 4.37 (m, 4 H), 4.19 (d, J = 11.6 Hz, 1 H), 3.90 (m, 4 H), 3.58 (m, 1 H), 3.41 (m, 1 H), 2.28 (d, J = 6.2 Hz, 1 H), 1.57 (s, 3 H), 1.51 (s, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.18 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 139.50, 136.77, 128.58, 128.52, 128.15, 128.13, 127.89, 117.10, 109.25, 99.71, 99.71, 79.57, 77.02, 76.80, 75.78, 75.32, 73.40, 70.58, 62.48, 62.16, 29.43, 28.44, 26.46, 18.85, 15.02; IR (neat) 3490 (broad), 2990, 2970, 1450, 1380, 1365, 1075, 860; HRMS for $C_{25}H_{37}O_8$ [M + H^+] calcd 465.2488, found 465.2512. Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81. Found: C, 64.31; H, 7.62.

In subsequent experiments, up to 30% of a triol was isolated resulting from hydrolysis of the 4′,6′-acetonide of the mannosyl unit of **21**.

(2*S*,3*R*,4*R*)-2-(Benzyloxy)-4-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]-5-hexen-3-ol (22). A solution of **6** (1.6 g, 2.7 mmol) in CH_2Cl_2 (2 mL) was added via cannula to a −23 °C solution of (*S*)-**19** (300 mg, 1.8 mmol) and $MgBr_2{\cdot}Et_2O$ (517 mg, 2.0 mmol) in CH_2Cl_2 (18 mL). The resulting solution was allowed to warm to room temperature and stirred for 90 min. The mixture was then diluted with saturated $NaHCO_3$ (25 mL), 10% KF solution (40 mL), and Et_2O (30 mL) and stirred vigorously for 1 h. The organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (1:1, Et_2O:hexanes) provided **22** (523 mg, 65% yield) as a clear oil: $[\alpha]^{25}_D$ = +40.0 (c = 0.6, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 7.14 (m, 5 H), 5.75 (m, 1 H), 5.48 (s, 1 H), 5.13 (ddd, J = 17.5, 1.1, 0.8 Hz, 1 H), 4.94 (ddd, J = 10.5, 1.1, 0.8 Hz, 1 H), 4.37 (m, 3 H), 4.26 (dd, J = 7.0, 7.2 Hz, 1 H), 4.08 (d, J = 11.6 Hz, 1 H), 3.97 (m, 3 H), 3.88 (m, 1 H), 3.78 (dd, J = 9.9, 9.7 Hz, 1 H), 3.43 (m, 1 H), 3.38 (m, 1 H), 2.53 (d, J = 6.4 Hz, 1 H), 1.55 (s, 3 H), 1.50 (s, 3 H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.11 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 138.93, 136.60, 128.54, 128.54, 127.91, 127.91, 127.87, 117.18, 109.25, 99.67, 99.54, 81.46, 77.41, 76.83, 75.78, 74.19, 73.42, 70.64, 62.47, 62.22, 29.41, 28.41, 26.40, 18.87, 16.00; IR (neat) 3480 (broad), 2990, 2965, 1450, 1380, 1365, 1215, 1065, 910 cm^{-1}; HRMS for $C_{25}H_{37}O_8$ [M + H^+] calcd 465.2488, found 465.2497. Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81. Found: C, 64.67; H, 7.82.

Adduct **22** was also prepared in 61% yield as the major component of a 5:1 (**22**:**23**) mixture from the $BF_3{\cdot}Et_2O$-promoted reaction of **6** and (*S*)-**19** following the procedure described for the synthesis of **8**. Diastereomers **22** and **23** were separated by silica gel chromatography (9:1, $CHCl_3$:acetone): R_f 0.50 for **22**, R_f 0.45 for **23** (1:1 EtOAc:hexanes). Partial data for **23**: ^1H NMR (400 MHz, C_6D_6) δ 7.15 (m, 5 H), 5.91 (ddd, J = 17.5, 10.5, 7.5 Hz, 1 H), 5.33 (s, 1 H), 5.12 (ddd, J = 17.5, 1.0 Hz, 1 H), 5.01 (dd, J = 10.5, 1.0 Hz, 1 H), 4.40 (m, 1 H), 4.35 (A of AB, 1 H), 4.17 (dd, 1 H), 4.12 (B of AB, 1 H), 4.00–3.87 (multiple

(31) Best results were obtained when freshly distilled $BF_3{\cdot}Et_2O$ was used.

(32) KOt-Bu in MeOH was added to neutralize with $BF_3{\cdot}Et_2O$ before the reactions were worked up. If this step was omitted, isolated yields of homoallyl ethers were often much lower than reported in the text, and products resulting from hydrolysis of one or both of the acetonide units of the mannosyl auxiliary were obtained.

(33) 2,6-Di-*tert*-butyl-4-methylpyridine was added to minimize cleavage of the acetonide units prior to workup. We subsequently determined that a better protocol involved adding KO^{t}Bu in MeOH before workup (see procedure for preparation of **8**).

overlapping signals, 5 H), 3.64 (m, 1 H), 3.47 (m, 1 H), 2.62 (d, 1 H), 1.55 (s, 3 H), 1.50 (s, 3 H), 1.33 (s, 3 H), 1.28 (d, 3 H), 1.26 (s, 3 H).

(2*S*,3*R*,4*S*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-bis(benzyloxy)-5-[(2,3:4,6-di-*O*-isopropylidene-α-D-*manno*-pyranosyl)oxy]hept-6-en-4-ol (27). $BF_3{\cdot}Et_2O$ (119 μL, 0.96 mmol)[31] was added dropwise to a −78 °C solution of (*R*)-**26**[5d] (100 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL). The resulting solution was stirred for 10 min, and then a solution of stannane **6** (284 mg, 0.48 mmol) in CH_2Cl_2 (1.2 mL) was added dropwise via cannula. The resulting mixture was stirred at −78 °C for 3 h, and then a mixture of t-BuOK (323 mg, 2.9 mmol) in MeOH (3 mL) was added and the solution was allowed to warm to room temperature. The resulting mixture was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (10 mL) and H_2O (2 × 10 mL). The organic solution was dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel chromatography (30% EtOAc in hexanes) provided **27** (125 mg, 73% yield) as a clear oil: $[\alpha]^{25}_D = 16.8°$ (*c* = 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 10 H), 5.44 (ddd, *J* = 17.3, 10.4, 8.0 Hz, 1 H), 5.18 (ddd, *J* = 17.3, 1.3, 0.8 Hz, 1 H), 5.15 (dd, *J* = 10.4, 1.3 Hz, 1 H), 5.11 (s, 1 H), 4.70 (AB, J_{AB} = 11.3 Hz, Δν = 50.4 Hz, 2 H), 4.56 (AB, J_{AB} = 11.3 Hz, Δν = 30.0 Hz, 2 H), 4.20–4.11 (m of overlapping signals, 3 H), 3.84 (s, 2 H), 3.80–3.55 (complex region of overlapping signals, 8 H), 1.54 (s, 3 H), 1.50 (s, 3 H), 1.42 (s, 3 H), 1.34 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100.6 HHz, $CDCl_3$) δ 137.83, 137.83, 136.43, 128.47, 128.47, 128.45, 128.45, 128.33, 128.33, 127.98, 127.93, 127.93, 127.86, 117.26, 109.33, 99.58, 98.93, 80.39, 79.01, 76.50, 76.13, 74.94, 74.08, 73.11, 72.77, 72.62, 61.98, 61.53, 61.49, 29.03, 28.16, 26.17, 25.83, 25.83, 25.83, 18.76, 18.13, −5.45, −5.49; IR ($CHCl_3$) 3541, 3010, 2981, 1454, 1384, 1244, 1218, 1084, 839; HRMS for $C_{39}H_{59}O_{10}Si$ [M + H$^+$] calcd 715.3877, found 715.3925.

(2*R*,3*S*,4*S*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-bis(benzyloxy)-5-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]hept-6-en-4-ol (28) and (2*R*,3*S*,4*R*,5*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-bis(benzyloxy)-5-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]hept-6-en-4-ol (29). $BF_3{\cdot}Et_2O$ (119 μL, 0.96 mmol)[31] was added dropwise to a −78 °C solution of (*S*)-**26**[5d] (100 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL). The resulting solution was stirred for 10 min, and then a solution of **6** (284 mg, 0.48 mmol) in CH_2Cl_2 (1.2 mL) was added dropwise via cannula. The resulting mixture was stirred at −78 °C for 3 h, and then a solution of t-BuOK (323 mg, 2.9 mmol) in MeOH (3 mL) was added. The mixture was then diluted with EtOAc (50 mL) and extracted with saturated $NaHCO_3$ (10 mL) and H_2O (2 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (30% EtOAc in hexanes) provided a 2:1 mixture of **28** and **29** (118 mg, 69% combined yield).

Data for 28: R_f 0.45 (3:1 hexanes:EtOAc); $[\alpha]^{25}_D = +13.6°$ (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 7.33–7.08 (m, 10 H), 5.75 (ddd, *J* = 17.3, 10.5, 7.8 Hz, 1 H), 5.53 (s, 1 H), 5.05 (ddd, *J* = 17.3, 1.5, 0.8 Hz, 1 H), 4.92 (dd, *J* = 10.5, 1.5 Hz, 1 H), 4.57 (AB, J_{AB} = 11.8 Hz, Δν = 53.3 Hz, 2 H), 4.50 (AB, J_{AB} = 12.9 Hz, Δν = 105.0 Hz, 2 H), 4.35 (m, 2 H), 4.26 (t, 1 H), 4.04–3.74 (complex set of overlapping signals, 9 H), 2.56 (broad d, 1 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.31 (s, 3 H), 1.21 (s, 3 H), 0.97 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.46, 138.11, 135.68, 128.40, 128.40, 128.33, 128.33, 127.97, 127.97, 127.83, 127.83, 127.81, 127.60, 118.65, 109.39, 99.61, 98.99, 81.25, 80.43, 76.42, 76.04, 74.89, 73.54, 72.91, 72.65, 72.38, 62.59, 61.57, 61.46, 29.03, 28.17, 26.15, 25.89, 25.89, 25.89, 18.75, 18.23, −5.38, −5.40; IR ($CHCl_3$) 3563 (broad), 3007, 2931, 2858, 1737, 1463, 1373, 1225, 1086, 937, 908, 839 cm^{-1}; HRMS for $C_{39}H_{59}O_{10}Si$ [M + H$^+$] calcd 715.3877, found 715.3848. Anal. Calcd for $C_{39}H_{58}O_{10}Si$: C, 65.52; H, 8.17. Found: C, 65.39; H, 8.27.

Data for 29: R_f 0.40 (3:1 hexanes:EtOAc); $[\alpha]^{25}_D = +8.2°$ (*c* = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 10 H), 5.85 (ddd, *J* = 17.3, 10.3, 8.5 Hz, 1 H), 5.35 (dd, *J* = 10.3, 1.6 Hz, 1 H), 5.28 (dd, *J* = 17.3, 1.6 Hz, 1 H), 5.17 (s, 1 H), 4.71 (AB, J_{AB} = 11.6 Hz, Δν = 44.5 Hz, 2 H), 4.58 (s, 2 H), 4.31 (dd, *J* = 8.6, 3.2 Hz, 1 H), 4.21 (A of ABX, J_{AB} = 7.6 Hz, J_{AX} = 0.0 Hz, 1 H), 4.17 (B of ABX, J_{AB} = 7.6 Hz, J_{BX} = 7.6 Hz, 1 H), 3.86–3.67 (complex region of overlapping signals, 9 H), 3.18 (s, broad, 1 H), 1.54 (s, 3 H), 1.50 (s, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.08, 138.07, 133.89, 128.45, 128.45, 128.38, 128.38, 128.18, 128.18, 127.89, 127.69, 127.62, 127.62, 120.78, 109.34, 99.62, 94.47, 79.18, 77.20, 76.75, 76.38, 74.79, 73.44, 73.20, 72.75, 72.68, 62.11, 61.93, 61.93, 29.00, 28.14, 26.16, 25.87, 25.87, 25.87, 18.78, 18.16, −5.45, −5.45; IR ($CHCl_3$) 3573, 3478 (broad), 2996, 2931, 2858, 1497, 1463, 1384, 1245, 1172, 1087, 940, 851 cm^{-1}; HRMS for $C_{39}H_{59}O_{10}Si$ [M + H$^+$] calcd 715.3877, found 715.3872.

(2*R*,3*S*,4*S*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-bis(benzyloxy)-5-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]hept-6-en-4-ol (28). A solution of aldehyde (*S*)-**26** (50 mg, 0.12 mmol) in CH_2Cl_2 (500 μL) was treated with $MgBr_2{\cdot}Et_2O$ (62 mg, 0.24 mmol). A solution of **6** (85 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL) was added and the resulting solution stirred at room temperature for 6 h. Saturated $NaHCO_3$ solution (3 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel chromatography (3:1 hexanes:EtOAc) provided exclusively alcohol **20** (55 mg, 65% yield). This material was identical in all respects to the major product obtained in the $BF_3{\cdot}Et_2O$-mediated mismatched reaction of (*S*)-**26** and **6** described in the preceding experimental procedure.

(2*R*,3*S*,4*S*)-2-(Benzyloxy)-4-[(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)oxy]-5-hexen-3-ol (41). $MgBr_2{\cdot}Et_2O$ (519 mg, 2.0 mmol) was added to a −23 °C solution of (*R*)-**19** (300 mg, 1.8 mmol) in CH_2Cl_2 (19 mL). This mixture was stirred for 15 min, and then a solution of **6** (1.6 g, 2.7 mmol) in CH_2Cl_2 (1 mL) was added dropwise via cannula. The resulting mixture was allowed to warm to 0 °C and then stirred for 20 min. The mixture was diluted with ether (30 mL) and saturated $NaHCO_3$ (25 mL) and treated with 10% KF solution (40 mL). The resulting mixture was stirred vigorously for 1 h, and then the aqueous layer was separated and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 Et_2O:hexanes) which provided **41** (626 mg, 80% yield) as a clear colorless oil: $[\alpha]^{25}_D = +2.1°$ (*c* = 1.8, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 7.19 (m, 5 H), 5.73 (m, 1 H), 5.35 (s, 1 H), 5.11 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.06 (dd, *J* = 10.2, 1.6 Hz, 1 H), 4.36 (m, 4 H), 4.13 (d, *J* = 11.8 Hz, 1 H), 3.95 (m, 3 H), 3.78 (dd, *J* = 9.7, 9.4 Hz, 1 H), 3.59 (dd, *J* = 6.2, 4.6 Hz, 1 H), 3.48 (d, *J* = 4.8 Hz, 1 H), 2.93 (d, *J* = 5.1 Hz, 1 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.33 (s, 3 H), 1.24 (s, 3 H), 1.14 (s, 3 H), 1.14 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 138.98, 134.58, 128.54, 128.54, 127.91, 127.76, 127.76, 119.85, 109.18, 99.73, 99.45, 78.64, 77.10, 75.59, 74.71, 73.41, 70.80, 62.60, 62.47, 29.35, 28.36, 26.39, 26.35, 18.84, 15.83; IR (neat) 3495 (broad), 2995, 2970, 1490, 1450, 1380, 1365, 1220, 1070, 855, 735 cm^{-1}; HRMS for $C_{25}H_{37}O_8$ [M + H$^+$] calcd 465.2488, found 465.2440. Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81. Found: C, 64.47; H, 7.82.

Representative Procedure for Hydrolysis of the Mannosyl Auxiliary: (3*R*,4*R*,5*S*)-5-Methylhex-1-ene-3,4,6-triol 3,4,6-Triacetate (10). A solution of **8** (55 mg, 0.11 mmol) in MeOH (1.5 mL) was treated with 1 N HCl (1.5 mL) and heated at 70 °C for 48 h. The resulting solution was cooled to room temperature and neutralized with 1 N NaOH. The resulting mixture was concentrated repeatedly from CH_3CN to remove water azeotropically. The resulting solid was triturated with MeOH (15 mL) and the filtrate concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and treated with Ac_2O (0.25 mL, 2.6 mmol), Et_3N (0.40 mL, 2.9 mmol), and DMAP (ca. 2 mg). The resulting mixture was stirred at room temperature for 8 h and then was diluted with EtOAc (45 mL) and extracted with saturated $NaHCO_3$ (2 × 10 mL). The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude material by silica gel chromatography (4:1 hexanes:EtOAc) provided triacetate **10** (20 mg, 67% yield) as a clear oil: $[\alpha]^{25}_D = +31.8°$ (*c* = 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (ddd, *J* = 17.2, 10.7, 6.9 Hz, 1 H), 5.41 (dd, *J* = 6.9, 6.9 Hz, 1 H), 5.39 (ddd, *J* = 17.2, 1.0, 1.0 Hz, 1 H), 5.31 (dd, *J* = 10.7, 1.0 Hz, 1 H), 5.19 (dd, *J* = 7.2, 4.0 Hz, 1 H), 3.95 (A of ABX, J_{AB} = 11.2 Hz, J_{AX} = 7.7 Hz, 1 H), 3.86 (B of ABX, J_{AB} = 11.2 Hz, J_{BX} = 6.7 Hz, 1 H), 2.16 (m, 1 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.90, 170.21, 169.86, 132.16, 119.99, 74.21, 72.78, 65.55, 33.18, 20.96, 20.80, 20.69, 11.02; IR ($CHCl_3$) 3031, 2975, 1737, 1470, 1426, 1371, 1251, 1025, 988, 947, 909; LRMS *m/e* (relative intensity) 213 (98), 173 (24), 153 (15), 131 (93), 113 (64), 84 (24), 71 (100); HRMS for $C_{13}H_{21}O_6$ [M + H$^+$] calcd 273.1338, found 273.1388.

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Supplementary Material Available: Details of the stereostructure assignments for **9**, **21–24**, **27**, **29**, and **41** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.