(M^+ - HOAc). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.78; H, 8.23.

A solution of the above acetate (89 mg, 0.44 mmol) in 0.5 mL of MeOH containing 0.05 mL of HOAc was hydrogenated over 13 mg of 5% Rh/Al_2O_3 under atmospheric hydrogen. When complete as indicated by TLC analysis, the mixture was filtered through a pad of Celite and then chromatographed through a 30 × 150 mm flash silica gel column (3:1 hexane-ether) to afford 91 mg (98%) of (1*S*,2*S*)-1-cyclohexyl-2-methyl-1-butyl acetate that was used directly in the following experiment: R_f 0.35 (3:1 hexane-ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (dd, J = 9.0, 9.0 Hz, 1 H), 2.12 (br s, 3 H), 1.57-1.78 (m, 6 H), 1.36-1.50 (m, 1 H), 1.02-1.35 (m, 6 H), 0.91-0.99 (m, 1 H), 0.80-0.90 (m, 6 H).

The acetate prepared above (75 mg, 0.35 mmol) was dissolved in 5 mL of Et_2O and treated with $LiAlH_4$ (15 mg, 0.38 mmol) at 0 °C. The reacion was complete within a few minutes and quenched according to the method described for the preparation of **10d**. The crude product was filtered through a short plug of flash silica gel, yielding 51 mg (86%) of **17** that was identical with the sample prepared from **9d**. Because the $[\alpha]^{25}_D$ value is so small and, therefore potentially unreliable, the absolute configuration of **17** prepared from **9h** was verified by preparing the (*R*)- and (*S*)-MTPA esters, which were indistinguishable from those prepared from the **9d** derived sample of **17**.

Correlation of 10d and 10h. Synthesis of (1*S*,2*R*)-1-Cyclohexyl-2-methylbutan-1-ol (18). Syn homoallyl alcohols **10d** and **10h** were converted to **18** by using the methods described for the synthesis of **17**. Compound **18** prepared from (*R*,*R*)-**3** derived **10d** had $[\alpha]^{25}_D$ +4.8° (*c* = 0.81, $CHCl_3$) while that from (*R*,*R*)-**3** derived **10h** had $[\alpha]^{25}_D$ +5.0° (*c* = 1.12, $CHCl_3$). The absolute configurations of these compounds was further verified by the Mosher ester analysis. Data for **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (dd, J = 7.6, 3.8 Hz, 1 H), 1.96 (br d, J = 12.8 Hz, 1 H), 1.72-1.78 (m, 2 H), 1.59-1.67 (m, 2 H), 1.52-1.54 (m, 1 H), 1.37-1.42 (m, 2 H), 1.13-1.29 (m, 5 H), 0.93-1.01 (m, 2 H), 0.90 (dd, J = 7.7, 7.2 Hz, 3 H), 0.85 (d, J = 6.2 Hz, 3 H); IR (thin film) 3380 (br), 2910 (s), 2840 (s). 1445 (s), 1370 (m), 1115 (m), 1075 (m), 975 (s) cm^{-1}; mass spectrum (Cl, NH_3), m/z 169 (M^+ - 1). Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.40; H, 13.15.

(3*R*,4*S*)-3-Methyl-4-phenyl-1-butenyl acetate (acetate derivative of **10h**): R_f 0.36 (3:1 hexane-ether); $[\alpha]^{25}_D$ -31.9° (*c* = 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.33 (m, 5 H), 5.63 (ddd, J = 17.5, 10.5, 7.4 Hz, 1 H), 5.62 (d, J = 7.1 Hz, 1 H), 4.94 (d, J = 10.5 Hz, 1 H), 4.93 (d, J = 17.5 Hz, 1 H), 2.67 (dq, J = 7.4, 6.8 Hz, 1 H), 2.07 (s, 3 H), 1.03 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.0, 139.0, 138.9, 127.9, 127.6, 127.0, 115.5, 78.8, 42.8, 21.0, 15.2; IR (thin film) 2978, 1741, 1456, 1374, 1233, 1020, 918, 757, 700 cm^{-1}; mass spectrum, m/z 149 (M^+ - crotyl), 144 (M^+ - HOAc). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.73; H, 7.87.

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Acyclic Diastereoselective Synthesis Using Tartrate Ester Modified Crotylboronates. Double Asymmetric Reactions with α-Methyl Chiral Aldehydes and Synthesis of the C(19)-C(29) Segment of Rifamycin S

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Abstract: Double asymmetric reactions of the tartrate ester modified crotylboronates **1** and **2** and α-methyl chiral aldehydes are described. The reactions of the appropriate enantiomers of **1** and **2** with β-alkoxy-α-methylpropionaldehydes **11** provide adducts **12**, **13**, and **14** with a minimum diastereoselectivity of 90%, provided that the optimal hydroxyl protecting group is selected for **11**. Thus, TBDMS protected aldehyde **11a** is the optimal substrate for the matched double asymmetric reactions leading to **12a** and **14a**, while the TBDPS protected **11b** is the optimal precursor to **13b** and **15b** via mismatched double asymmetric reactions. A similar dependence of stereoselectivity on the protecting group is seen in the reactions of **11** and chiral allylboronate **16**. It is inferred from these and other data (c.f., $\sum\Delta\Delta G^{\ddagger}$ data provided in Table IV) that β-alkoxy aldehyde substituents have a significant, negative impact on the diastereoselectivity of the double asymmetric reactions of the tartrate allylboronates, especially those involving **2** and **16**. Additional insight into the existence of the "alkoxy effect" is provided by the double asymmetric reactions of **1**, **2**, and **16** with aldehyde **20** that lacks an offending β-alkoxy group. These experiments (Table V) show that the diastereoselectivity of the reactions of **20** especially with **2** and **16** ($\sum\Delta\Delta G^{\ddagger}$ = 1.7-1.8 kcal mol^{-1}) are significantly improved relative to those with **11** (typically $\sum\Delta\Delta G^{\ddagger}$ = 1.1-1.4 kcal mol^{-1}). Improvements in stereoselectivity of the allyl- and (*E*)-crotylborations of both **11** and **20** are also possible by using reagents **28** and **29** incorporating the more highly enantioselective *N*,*N*'-dibenzyl-*N*,*N*'-ethylenetartramide auxiliary previously developed in these laboratories (Table VI). Adduct **23** deriving from these studies has been converted into lactone **27**, a known precursor of the Prelog-Djerassi lactonic acid. An empirical model is presented that enables one to predict the situations in which **1** and **2** will be maximally effective in complex synthetic problems. Thus, dipropionate substructures **7** and **9** with anti relationships between branching methyl groups can be prepared with very high diastereoselectivity via matched double asymmetric reactions with the appropriate α-methyl chiral aldehyde substrate, while substructures **8** and **10** with syn relationships between methyl branches are more difficult to prepare via mismatched double asymmetric reactions. Moreover, the ease of preparation of **7** and **9**, and the difficulty with **8** and **10**, is expected to increase as the intrinsic diastereofacial preference of the chiral aldehyde increases. Accordingly, the number of bond constructions leading to 1,3-anti branching methyl relationships should be maximized when applying this technology in total synthesis, and the more difficult 1,3-syn branching methyl units should be introduced as early as possible. These principles are illustrated in a highly diastereoselective synthesis of the C(19)-C(29) segment of the ansa bridge of rifamycin S. This synthesis features four C-C bond forming reactions involving the chiral crotyl- and allylboronate technology and proceeds in 15% yield and with 78% stereoselectivity for the 16-step sequence originating from (*S*)-**11b**.

In the preceding paper we described the synthesis of tartrate ester modified crotylboronates **1** and **2** and defined the stereochemistry of their reactions with achiral aldehydes.[3] Our motivation to initiate synthetic studies in this area derived from the

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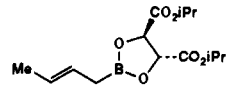
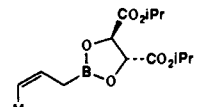
expectation that a group of highly enantioselective crotylboron reagents would provide a simple solution to the problem posed by the formal aldol extension of a chiral aldehyde by an additional propionaldehyde unit.[4,5]

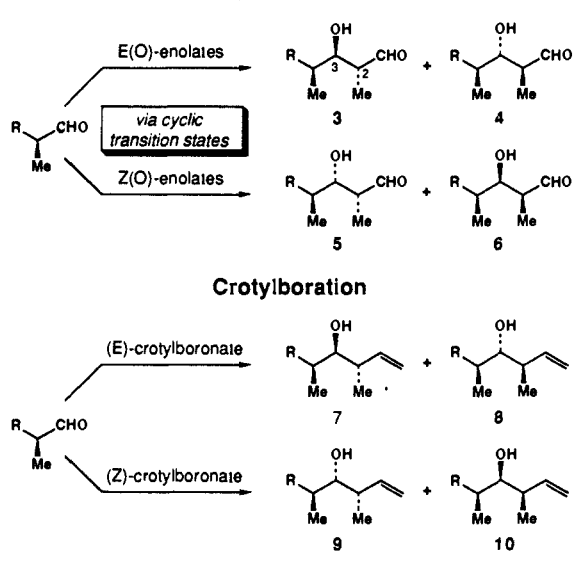


(R,R)-1



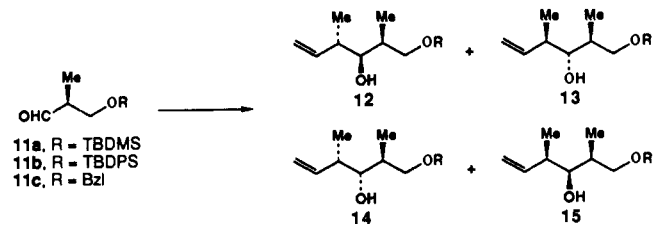
(R,R)-2

This classical problem in acyclic diastereoselective synthesis has attracted considerable attention owing to the widespread occurrence of propionate-derived units (e.g., -CHMe-CHOH-CHMe-CHOH-) as prominent structural features of macrolide, ansamycin, and many other biologically active natural products. While several multistep synthetic procedures for synthesis of functional equivalents **3–6** (or **7–10**) had appeared,[6] no totally



general one-step synthetic solution using either aldol or crotylmetal chemistry was available at the time our studies were initiated in 1983. Access to the 2,3-syn aldol diastereomers **5** and **6** was possible by using one of several highly enantioselective [Z-(O)]-propionate enolate equivalents,[7] but comparable success had not yet been achieved in the direct aldol construction of the 2,3-anti diastereomers **3** and **4**.[8,9] Hoffmann, however, had demonstrated

Table I. Reactions of **11** and Achiral Crotylmetal Reagents



entry	aldehyde	reagent	product ratios 12	13	14	15
1	**11a**[a]	pinacol (*E*)-crotylboronate	61	39	–	–
2	**11b**[a]	pinacol (*E*)-crotylboronate	62	38	–	–
3	**11c**[a]	pinacol (*E*)-crotylboronate	68	32	–	–
4	**11a**[a,b]	pinacol (*Z*)-crotylboronate	9	7	55	29
5	**11b**[a,b]	pinacol (*Z*)-crotylboronate	4	3	61	32
6	**11c**[a,b]	pinacol (*Z*)-crotylboronate	4	3	61	32
7[13b]	**11c**	$CH_3CH{=}CHCH_2I/CrCl_2$	61	39	–	–
8[13a]	**11a**	$CH_3CH{=}CHCH_2SnBu_3/BF_3$	–	–	5	95
9[13a]	**11c**	$CH_3CH{=}CHCH_2SnBu_3/MgBr_2$	2	7	81	10

[a] Reaction performed in toluene at 23 °C. [b] The pinacol (*Z*)-crotylboronate used in these reactions was of low isomeric purity (ca. 90%).

that chiral crotylboronates incorporating the *endo*-3-phenyl-*exo*-2,3-bornanediol auxiliary were capable of enhancing the diastereoselectivity of the crotylborations of chiral aldehydes at least in the matched double asymmetric pair.[5]

It was thus apparent to a number of investigators that a highly enantioselective (*E*)-crotylmetal reagent would provide a concise solution to the 2,3-anti aldol problem through the construction of 3,4-anti homoallyl alcohols **7** and **8**.[4,10,11] This thus became the primary focus of our research in crotylmetal chemistry.[11a] It was also clear that if a highly 3,4-syn selective (*Z*)-crotylmetal reagent could be developed, then totally generaly synthetic methodology would be available for the construction of **7–10**, and hence also **3–6**. We have contributed the tartrate crotylboronates **1** and **2** to this rapidly evolving area of research and have demonstrated that they constitute a pair of synthetically useful (*E*)- and (*Z*)-propionate enolate surrogates.[11]

(1) Portions of this research were performed at the Massachusetts Institute of Technology.

(2) Holder of an ACS Organic Division Fellowship, 1987–88, sponsored by Eli Lilly.

(3) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *J. Am. Chem. Soc.*, preceding paper in this issue.

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(5) (a) For pioneering studies of double asymmetric reactions of chiral crotylboronates and chiral aldehydes, see: Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218; Hoffmann, R. W.; Zeiss, H.-J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982**, *115*, 2357; Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320. (b) For a review of double asymmetric synthesis: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

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(9) For direct solutions to the anti aldol problem: (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (b) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Sooc.* **1985**, *107*, 5812. (c) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. (d) Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699. (e) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125. (f) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (g) Short, R. P.; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841.

(10) Several highly enantioselective chiral crotylmetal reagents with demonstrated utility in double asymmetric synthesis are described in the following papers. Leading references to other classes of chiral allylmetal reagents are provided in the literature cited in ref 3: (a) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 2013. (b) Ditrich, K.; Bube, T.; Stürmer, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1028. (c) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319 and 3701. (d) Garcia, J.; Kim, B.-M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831. (e) Hoffmann, R. W. Dresely, S. *Tetrahedron Lett.* **1987**, *28*, 5303. (f) Hoffmann, R. W.; Dresely, S.; Lanz, J. W. *Chem. Ber.* **1988**, *121*, 1501. (g) Hoffmann, R. W.; Dresely, S.; Hildebrandt, B. *Ibid.* **1988**, *121*, 2225. (h) Hoffmann, R. W.; Dresely, S. *Ibid.* **1989**, *122*, 903. (i) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Ibid.* **1989**, *122*, 1783. (j) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

(11) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (c) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953. (d) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. (e) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (f) Roush, W. R.; Palkowitz, A. D. *Ibid.* **1989**, *54*, 3009. (g) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *Ibid.* **1990**, *55*, 4109.

Table II. Reactions of **11** with Chiral Reagents **1** and **2**

entry	aldehyde[b]	reagent	yield, %[c]	product ratios[d] 12	13	14	15
1	**11a**	(*R,R*)-**1**	80	[97]	3	–	–
2	**11b**	(*R,R*)-**1**		82	16	1	2
3	**11c**	(*R,R*)-**1**		93	5	1	1
4[e]	**11a**	(*S,S*)-**1**		18	82	–	–
5	**11b**	(*S,S*)-**1**	85	11	88	1	–
6[e]	**11b**	(*S,S*)-**1**	77	10	[90]	–	–
7	**11c**	(*S,S*)-**1**		15	85	–	–
8	**11a**	(*S,S*)-**2**	71	–	4	[95]	1
9	**11b**	(*S,S*)-**2**		–	4	85	12
10	**11c**	(*S,S*)-**2**		–	3	88	9
11[g]	**11a**	(*R,R*)-**2**		12	2	45	41
12[f]	**11b**	(*R,R*)-**2**		4	1	32	63
13[g]	**11b**	(*R,R*)-**2**		9	3	24	[64]
14[f]	**11c**	(*R,R*)-**2**		2	–	46	52
15[g]	**11c**	(*R,R*)-**2**		8	2	45	45

[a] All reactions were performed in toluene (0.2 M) at −78 °C in the presence of 4-Å molecular sieves (typically 25–50 mg/mmol) with 1.5 equiv of reagent. [b] See ref 12a. [c] Combined yield of products from preparative scale experiments (see ref 12b). [d] Diastereomer ratios were determined by HPLC analysis (see Experimental Section). [e] Experiment performed with 99% isomerically pure **1**. [f] Experiments performed with 99% isomerically pure **2**. [g] Experiments performed with **2** prepared via the $(MeO)_2BF$ route (ref 3) that in retrospect had poor isomeric purity.

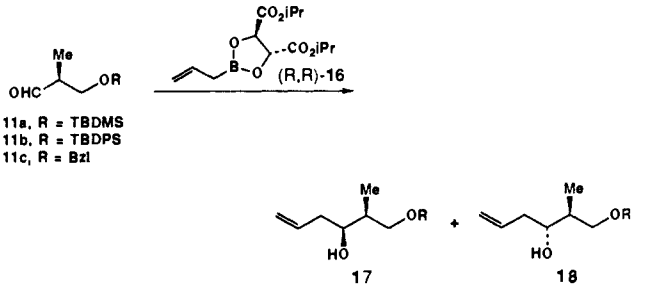
We describe here the double asymmetric reactions[5b] of **1** and **2** with several chiral α-methyl branched aldehydes and applications of this methodology towards the synthesis of the C(19)–C(29) segment of rifamycin S. Preliminary accounts of portions of this work have appeared.[11b,c] An empirical model is also presented that enables one to predict situations in which **1** and **2** will be maximally effective in complex synthetic problems. We believe that this paradigm will prove to be exceptionally useful in the analysis of complex synthetic targets, enabling one to predict the most efficient set of bond constructions to be pursued in the synthesis. This paradigm is illustrated in our analysis of the rifamycin S ansa chain stereochemical problem.

Reactions of 1 and 2 with Chiral α-Methyl Branched Aldehydes

We began by studying the reactions of **1** and **2** with β-alkoxy-α-methylpropionaldehydes **11**.[12,13] Use of chiral reagents **1** and **2** to achieve high diastereofacial selectivity is necessary here since **11** does not possess a sufficently large intrinsic diastereofacial bias in reactions with most achiral crotylmetal reagents.[14] Some typical results are summarized in Table I. These data show that only the 3,4-syn-4,5-syn diastereomer **15** is available with synthetically useful levels of diastereoselection, and then only by using a Type II BF_3 catalyzed crotylstannane reaction (entry 8).[15,16] With the achiral pinacol (*E*)- and (*Z*)-crotylboronates, diastereomers **12** (from the (*E*)-crotylboronate) and **14** (from the (*Z*)-crotyl reagent) are intrinsically favored, but are obtained with no better than 61–68% diastereoselectivity.

Results of reactions of **11a–c** with the tartrate crotylboronates **1** and **2** are summarized in Table II. Most of these experiments were performed by using **1** and **2** prepared via our original crotylpotassium/$FB(OMe)_2$ method and thus may well be unoptimized with respect to the minimization of minor diastereomers (e.g., compare entries 5–6 and 12–15).[3] Reactions were otherwise performed under standard conditions in toluene at −78 °C and were complete within 4 h (as determined by quenching analytical scale reactions with excess $NaBH_4$ in EtOH to consume any unreacted **11**). Preparative scale experiments were diluted with aqueous NaOH to hydrolyze DIPT and then products were iso-

Table III. Reactions of **11** and Allylboronates[a]



entry	aldehyde	reagent	yield, %	product ratios 17	18
1	**11a**	(*R,R*)-**16**	71	[89]	11
2	**11b**	(*R,R*)-**16**		79	21
3	**11c**	(*R,R*)-**16**		83	17
4	**11a**[b]	pinacol allylboronate		52	48
5	**11b**[b]	pinacol allylboronate		54	46
6	**11c**[b]	pinacol allylboronate		54	46
7	**11a**	(*S,S*)-**16**		19	81
8	**11b**	(*S,S*)-**16**		13	[87]
9	**11c**	(*S,S*)-**16**	72	20	80

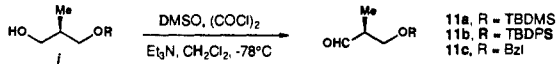
[a] See notes *a–d* of Table II. [b] These experiments were performed at 23 °C.

Table IV. Total Free Energy Swings, $\sum\Delta\Delta G^{\ddagger}$ (kcal mol^{-1}), for the Reactions of **11** and Allylboronates **1**, **2**, and **16**[a,b]

aldehyde	1	2	16
11a	2.0	1.7	1.4
11b	1.5	1.1	1.1
11c	1.8	0.9	1.2
c-$C_6H_{11}CHO$	(2.0)[b,c]	(1.8)[b,d]	(2.0)[b,c]
$TBDMSOCH_2CH_2CHO$	(1.95)[b,e]	(1.4)[b,f]	(1.3)[b,g]

[a] The total energy swing is defined as the sum of $\Delta\Delta G^{\ddagger}$(matched) and $\Delta\Delta G^{\ddagger}$(mismatched) for the reactions of a given aldehyde with both enantiomers of **1**, **2**, and **16** (refs 17, 18). [b] The data tabulated for c-$C_6H_{11}CHO$ and $TBDMSOCH_2CH_2CHO$ are two times the $\Delta\Delta G^{\ddagger}_{reagent}$ term determined in single asymmetric induction experiments (conventional % ee determinations). [c] For 87% ee (ref 3, 11g). [d] For 83% ee (ref 3). [e] For 85% ee (ref 3). [f] For 72% ee (ref 3). [g] For 66% ee (ref 17).

(12) (a) Aldehydes **11a–c** were prepared from methyl 3-hydroxy-2-methylpropionate, both enantiomers of which are commercially available (Aldrich). Standard literature methods were employed (e.g., (i) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (ii) Meyers, A. I.; Babiak, K. A.; Campbell, H. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015). The final step in each case was the Swern oxidation of alcohol i. The enantiomeric purity of crude **11** was >98% ee as determined by Mosher ester analysis of i recovered after $LiAlH_4$ reduction of **11**. Attempts to purify **11** by silica gel chromatography resulted in 5–7% racemization (85–90% ee). Since the diastereoselectivity of the reactions of **11** with **1** and **2** depends on the enantiomeric purity of **11**, crude aldehyde was used in all of the studies described in text.



(b) All yields are for two steps including the oxidation of i.

(13) (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (b) Lewis, M. D.; Kishi, Y. *Ibid.* **1982**, *23*, 2343.

(14) For a discussion of the factors that influence aldehyde diastereofacial selectivity in reactions of chiral aldehydes and achiral crotylboronates, see ref 4c and: (a) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966. (b) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

(15) For the mechanistic definitions of crotylmetal reagents: Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

(16) For other reactions of α-methyl aldehydes and tributylcrotylstannane/BF_3 that follow the same stereochemical course as entry 8 of Table I: (a) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (b) Suzuki, K.; Katayama, E.; Tomooka, K.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3707. (c) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645.

lated by chromatography. Stereochemical assignments for **12b,c**, **13b,c**, **14b,c**, and **15a–c** are based on ^{1}H NMR comparisons to spectral data for authentic samples kindly provided by Professor G. Keck,[13a] while the stereochemical assignments for **12a–14a** are based on mechanistic considerations and the similarities of their ^{1}H NMR spectra with stereochemical congeners in the TBDPS and benzyl ether protected series.

The data summarized in Table II show that three of the four diastereomers, **12**, **13** and **14**, are accessible with a minimum diastereoselectivity of 90% if care is taken to select the proper protecting group. Thus, the TBDMS group consistently gave the best results in the matched double asymmetric reactions leading to **12** and **14** (entries 1, 8), while diastereoselectivity in the mismatched double asymmetric combinations leading to diastereomers **13** and **15** was best when the TBDPS blocking group was employed (entries 6, 13). A similar pattern was observed in the reactions of **11a–c** and the diisopropyl tartrate modified allylboronate (**16**) (Table III).[11b,17]

The dependence of stereoselectivity on the hydroxyl protecting group was unexpected and is a phenomenon that we have not observed in the reactions of **11a–c** with the achiral pinacol crotyl- and allylboronates (Tables I, III) or in the reactions of tartrate allylboronate **16** and a series of achiral α-, β-, and γ-alkoxy substituted aldehydes.[17] Even more intriguing is that in many cases the enantioselectivity exerted by **1** and **2** (and **16** as well) in the reactions with **11** is much less than would be anticipated based on analogies drawn to the reactions of these chiral reagents with achiral aldehydes such as decanal or cyclohexanecarboxaldehyde.[3] This is most easily assessed by comparing the total free energy swing in diastereoselectivity, $\sum\Delta\Delta G^{\ddagger}$, for the set of matched and mismatched double asymmetric reactions.[18]

Total free energy swings for the reactions of aldehydes **11a–c** with reagents **1**, **2**, and **16** are summarized in Table IV. Also included are comparative $2 \times \Delta\Delta G^{\ddagger}_{R}$ values (e.g., for cyclohexanecarboxaldehyde and TBDMSOCH$_2$CH$_2$CHO) that provide an estimation of the level of stereoselectivity (in energetic terms) that would be anticipated in these double asymmetric reactions if **11a–c** were ideal allylboration substrates.[17,18] These data show that the reactions of **11a** and **11c** with **1** and **11a** with **2** are relatively well behaved compared to the cyclohexanecarboxaldehyde single asymmetric induction model, but that all of the other double asymmetric reactions in Tables II and III are not. The total free energy swings realized in the reactions of **11** and allylboronate **16** are better modeled by using a $\Delta\Delta G^{\ddagger}_{R}$ term obtained from % ee experiments with TBDMSOCH$_2$CH$_2$CHO. The data for the reactions of **11b** and **11c** and (*Z*)-crotylboronate **2**, however, are poorly modeled even by the TBDMSOCH$_2$CH$_2$CHO analogy.

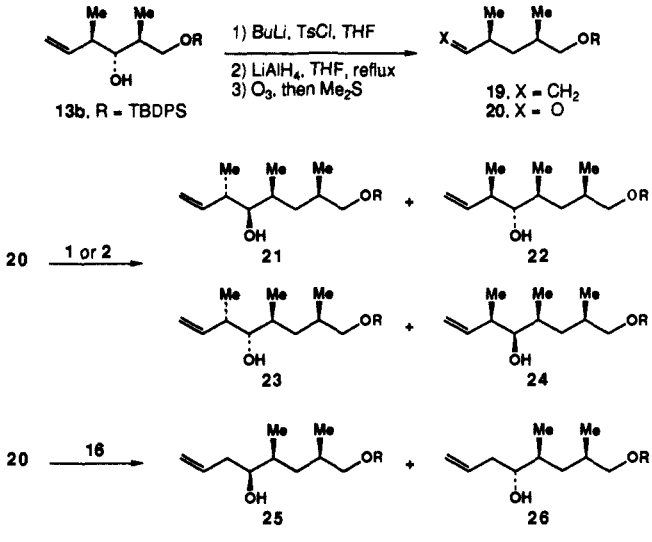
These and additional data presented elsewhere[17] strongly suggest that a β-alkoxy aldehyde substituent has a significant, negative effect on the absolute level of asymmetric induction realized in the asymmetric crotyl and allylborations of **1** and especially of **2** and **16**. Curiously, a similar tendency is not seen in the reactions of alkoxy-substituted aldehydes and the crotyl and allyldiispinocampheylboranes developed by Brown,[10c,j] or apparently with any of the other recently introduced chiral crotylboron reagents.[10] We believe that the origin of this "alkoxy effect" is electronic and not steric in nature.[17] In any event, this effect is likely to restrict most successful applications of **1**, **2**, and **16** in reactions with α-methyl-β-alkoxyaldehydes, especially those with large intrinsic diastereofacial biases, to cases of matched double diastereoselection (vide infra).

Table V. Diastereoselectivity Data for the Reactions of 20 with 1, 2 and 16[a]

reagent	yield, %	21	22	23	24	25	26	$\sum\Delta\Delta G^{\ddagger}$[c]
(*R,R*)-**1**	56	[≥98]	<2	–	–	–	–	≥2.1
(*S,S*)-**1**	55	16	[84]	(<1)	–	–	–	
(*S,S*)-**2**	51	(<1)[d]		[94]	6	–	–	1.8
(*R,R*)-**2**	52	6[d]		16	[78]	–	–	
(*R,R*)-**16**	68	–	–	–	–	[92]	8	1.7
(*S,S*)-**16**	67	–	–	–	–	13	[87]	

[a] Reactions were performed in toluene at −85 to −90 °C by using **1** and **2** of ≥98% isomeric purity. [b] Combined yield of products isolated chromatographically. [c] Total free energy swing (kcal mol^{-1}); see ref 18. [d] Combined amount of **21** and **22**.

Scheme I

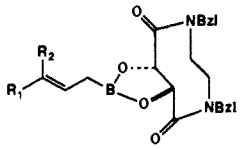


In order to gain additional insight into the β-alkoxy effect, we examined the asymmetric crotyl and allylborations of **20** that lacks the potentially offending β-alkoxy substituent. The synthesis of **20** and results of its reactions with **1**, **2**, and **16** are summarized in Scheme I and Table V. These data show that the matched double asymmetric reactions of **20** and (*R,R*)-**1** provides **21** with ≥98% selectivity (only one product detected) while the mismatched double asymmetric reaction with (*S,S*)-**1** provides **22** as the major product of an 84:16 mixture. It should be noted that the intrinsic diastereofacial selectivity of **20** [78:22 in favor of **21**; measured at −78 °C via the reaction with the meso diisopropyl tartrate (*E*)-crotylboronate] is somewhat greater than that of **11**, consequently it is easier to obtain very high matched double diastereoselection for **21** and correspondingly more difficult to achieve high stereoselectivity for **22** in the mismatched double asymmetric reaction. The total free energy swing ($\sum\Delta\Delta G^{\ddagger}$) for this pair of reactions is at least 2.1 kcal/mol, a value that compares well with expectations on the basis of the enantioselectivity of **1** in reaction with achiral aliphatic aldehydes (Table IV). The reactions of **20** and (*R,R*)-**2** or (*S,S*)-**2** provide **23** and **24** with 94% and 78% stereoselectivity, respectively. The latter result (83% stereoselectivity if the data are corrected for-amount of **21** and **22** also produced) is particularly gratifying in view of our inability to prepare **15** from aldehyde **11** with any significant degree of diastereoselection (Table II, entries 12–15). The $\sum\Delta\Delta G^{\ddagger}$ for the pair of double asymmetric reactions involving **2** is 1.8 kcal mol^{-1}, a value again consistent with expectations based on the enantioselectivity of **2** and achiral aliphatic aldehydes such as cyclohexanecarboxaldehyde. Finally, the reactions of **20** and the two enantiomers of allylboronate **16** are also more selective (compare $\sum\Delta\Delta G^{\ddagger}$ terms) than any of the reactions of **16** and alkoxy substituted aldehydes **11**.

(17) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.

(18) The total free energy swing of double diastereoselectivity, $\sum\Delta\Delta G^{\ddagger}$, is the sum of $\Delta\Delta G^{\ddagger}_{M}$ and $\Delta\Delta G^{\ddagger}_{MM}$ for the matched and mismatched double asymmetric reactions, respectively, and defines the total influence of the chiral reagent on the chiral substrate in the pair of double asymmetric reactions in energetic terms. The *average diastereoselectivity*, $\Delta\Delta G^{\ddagger}_{R(avg)}$, exerted by the chiral reagent in each of the pair of double asymmetric reactions is determined by dividing $\sum\Delta\Delta G^{\ddagger}$ by 2. Average diastereoselectivity terms [$\Delta\Delta G^{\ddagger}_{R(avg)}$] so determined are functionally equivalent to $\Delta\Delta G^{\ddagger}_{R}$ determined from single asymmetric induction experiments of the chiral reagent with an achiral substrate (see ref 17 for a discussion). That is, determination of the total free energy swing ($\sum\Delta\Delta G^{\ddagger}$) enables one to quantitatively assess the behavior of the chiral reagent in a set of double asymmetric reactions. This point is discussed more fully in ref 17.

Table VI[a]

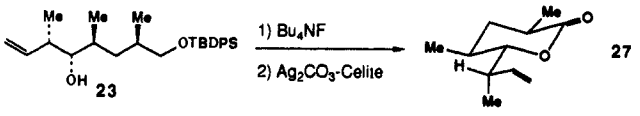


28, R_1 = Me, R_2 = H
29, R_1 = R_2 = H

entry	reagent	aldehyde	yield, %	products (selectivity)
1	(*R*,*R*)-**28**	**11b**	26	**12b** (92%), **13b** (7%), **14b** (1%)
2	(*S*,*S*)-**28**	**11b**	27	**12b** (4%), **13b** (96%)
4	(*R*,*R*)-**28**	**20**	51	**21** (>99%), **22** (<1%)
5	(*S*,*S*)-**28**	**20**	44	**21** (12%), **22** (88%)
6	(*R*,*R*)-**29**	**20**	82	**25** (97%), **26** (3%)
7	(*S*,*S*)-**29**	**20**	76	**25** (7%), **26** (93%)

[a] All reactions were performed at −78 °C in toluene in the presence of 4-Å for 3–4 days. As the reactions were not complete under these conditions (due largely to the poor solubility of **28** and **29**), the reactions were terminated by the addition of excess, precooled $NaBH_4$ in EtOH. The primary alcohols corresponding to **11b** and **20** were recovered: 58–63% in entries 1, 2; 39–41% in entries 3, 4; and 10–15% in entries 5, 6. Thus, the total mass recovery was 85–92% in each experiment.

The stereochemistry of adduct **23** was established by conversion to lactone **27** which has previously served as an intermediate in several syntheses of the Prelog–Djerassi lactonic acid.[19] Stereochemical assignments for all other compounds in this series are based on the well established stereochemistry of the reactions of **1**, **2**, and **16** with other aldehydes, both chiral and achiral.[3,11,17]

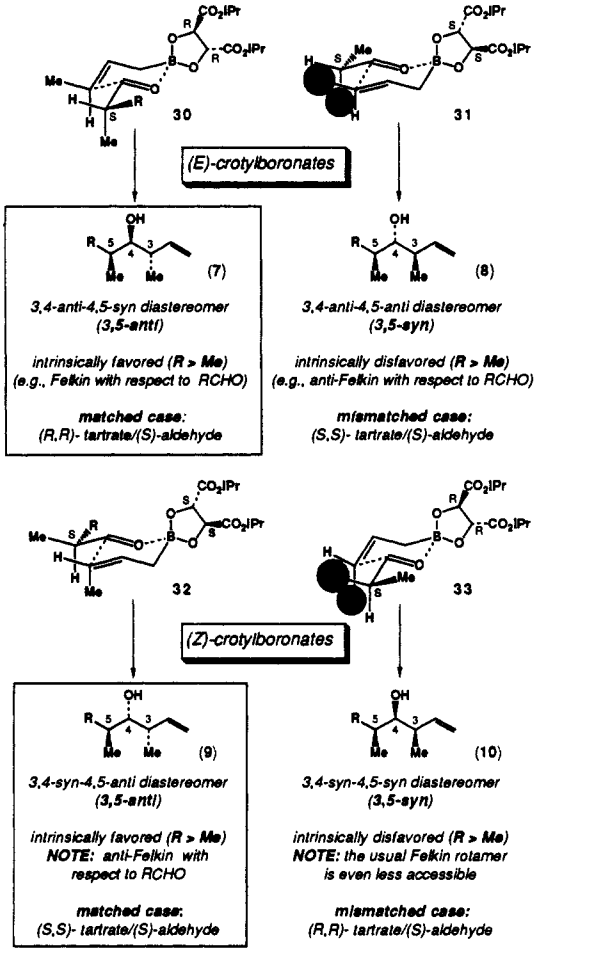


It is possible to achieve higher levels of diastereoselection in the allyl and crotylborations of **11** and **20** by using reagents **28** and **29** that incorporate the more highly enantioselective tartramide auxiliary previously developed in these laboratories.[3,20] Thus, for example, the reactions of aldehyde **11b** with (*R*,*R*)- and (*S*,*S*)-**28** provide **12b** and **13b** with 92% and 96% selectivity, respectively, compared to 82% and 90% diastereoselectivity via the reactions with (*R*,*R*)- and (*S*,*S*)-**1** (Table II). Similarly, selectivity in the reactions of **20** with **28** and **29** are much improved relative to those with **1** and **16** (compare entries 4–7 of Table VI with entries 1, 2, 5, and 6 of Table V). Improvements in selectivity were not realized, however, by using the (*Z*)-crotyl isomer of **28** as a substitute for **2**. Reasons for the inconsistent and problematic behavior of the (*Z*)-crotyl derivative are unclear at present. Additional experiments along these lines await the development of chiral reagents with solubility and reactivity characteristics more favorable than **28**–**29**.[3,20]

Transition-State Analysis: A Paradigm for Predicting High Selectivity Applications of the Tartrate Crotylboronates in Organic Synthesis

Transition states for the reactions of the tartrate crotylboronates and α-Me chiral aldehydes appear in Scheme II. Previous investigations of the reactions of α-Me chiral aldehydes and achiral crotylboronates have revealed that diastereomers **7** and **9**, each with an anti relationship between the branching methyl groups at C(3) and C(5), are favored (c.f., Table I, entries 1–6).[4c,14] This intrinsic diastereofacial preference for reaction through transition states corresponding to **30** and **32** derives from the nonbonded interactions that the crotyl methyl group experiences with the aldehyde R substituent in disfavored transition states **31** and **33**;

Scheme II. Transition States for Double Asymmetric Reactions of 1 and 2 and Chiral Aldehydes



As the steric requirements of R increase relative to Me, that is, as the intrinsic diastereofacial preference of the chiral aldehyde becomes increasingly large, it becomes increasingly difficult to synthesize the 3,5-syn diastereomers 8 and 10 by mismatched double asymmetric reactions. The 3,5-anti diastereomers 7 and 9, however, become trivially easy to synthesize with exceptional diastereoselection via matched double asymmetric reactions.

the extent of relative diastereoselection in fact increases as the steric requirements of R increase relative to Me.[4c,14a] It is noted further that while transition state **30**, leading to the 3,4-anti-4,5-syn diastereomer **7** from an (*E*)-crotylboronate, corresponds to Felkin selectivity with respect to the chiral aldehyde, the Felkin–Anh model fails to predict the major diastereomer of the reactions of α-methyl chiral aldehydes and achiral (*Z*)-crotylboronates.[4c,14a] The Felkin–Anh model is consistently violated in the reactions of α-methyl chiral aldehydes and (*Z*)-crotylboronates.

The data summarized in Tables II and V establish that it is possible to increase significantly the diastereoselectivity for the 3,4-anti-4,5-syn diastereomer **7** (from (*E*)-crotylboronates) and the 3,4-syn-4,5-anti diastereomer **9** (from (*Z*)-crotylboronates) by coupling the intrinsic diastereofacial preference of the substrate with the previously established[3] enantioselectivity of the tartrate auxiliary in reagents **1** and **2**. Thus, an (*R*,*R*)-**1**/*S* aldehyde combination constitutes a matched pair in transition state **30**, while in the (*Z*)-crotyl series it is an (*S*,*S*)-reagent/(*S*)-aldehyde combination that is the matched pair.

Intrinsically disfavored diastereomers **8** and **10** are accessible with preparatively useful stereoselectivity only by using the enantioselectivity of the chiral auxiliary to override the diastereofacial preference of the chiral aldehyde substrate; the relative absolute configurations of the two reactants in these mismatched double asymmetric pairings are defined in Scheme II. It must be stressed, however, that as the intrinsic diastereofacial preference of the substrate increases, it becomes increasingly difficult to prepare diastereomers **8** and **10**. This is particularly problematic for

(19) (a) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (b) Hoffmann, R. W.; Zeiss, H.-J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982**, *115*, 2357.

(20) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

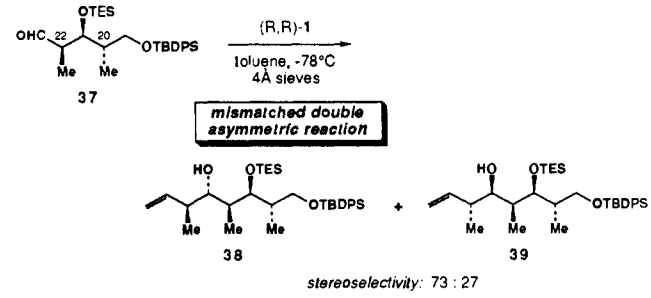
aldehydes possessing conformationally unconstrained β-alkoxy groups that detract from the enantioselectivity exerted by the tartrate auxiliary.[17] The reverse situation of source pertains for diastereomers **7** and **9**: these structures become overwhelmingly easy to prepare via matched double asymmetric reactions as the intrinsic diastereofacial preference of the aldehyde substrate increases.

A simple paradigm for predicting the applicability of the tartrate crotylboronates in complex synthetic problems emerges from this analysis. *Polypropionate substructures with 1,3-anti relationships between branching methyl groups are prepared with excellent diastereoselectivity via matched double asymmetric reactions. On this basis, the number of bond constructions leading to 1,3-anti relationships should be maximized when applying this technology in total synthesis.* A corollary is that the more difficult 1,3-syn methyl relationships should be introduced as early in a synthesis as possible. These principles are illustrated in our synthesis of the C(19)–C(29) segment of the ansa bridge of rifamycin S that is described in the following section.

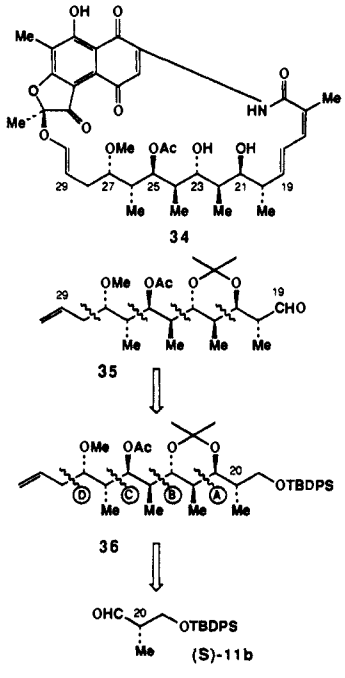
Synthesis of the C(19)–C(29) Segment of Rifamycin S

Rifamycin S (**34**) is a well-known member of the ansamycin antibiotic group.[21] We decided to develop a synthesis of **35** corresponding to the stereochemically rich C(19)–C(29) segment of the ansa chain as a means of probing the synthetic utility specifically of the chiral (*E*)-crotylboronate **1**.[11c,22]

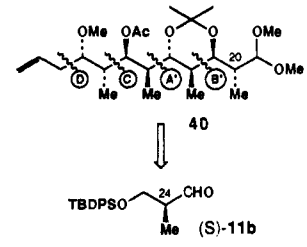
An initial analysis focused on the strategic bond disconnections A–D indicated in **36**. According to the stereochemical analysis presented in the preceding section, we anticipated that bond A would be assembled by the matched double asymmetric reaction of (*S*)-**11b** and (*S,S*)-(*Z*)-crotylboronate **2**. Similarly, we anticipated that bonds C and D could be established with high diastereoselectivity by using (*S,S*)-**1** and (*R,R*)-**16**, respectively, in sequential matched double asymmetric reactions. Only bond B would require a mismatched double asymmetric pairing (c.f., the syn relationship between the C(22) and C(24) methyl groups), and consequently this disconnection was viewed as the most critical of the four. In the event, aldehyde **37** representing the C(19)–C(23) segment was prepared from the 3,4-anti-4,5-syn dipropionate **14b** by a standard two-step operation ((i) Et_3SiCl, Et_3N, DMF; (ii) O_3, MeOH, −78 °C; Me_2S quench). Dipropionate **14b** had previously been obtained as the major product of the matched double asymmetric reaction between **11b** and (*S,S*)-**2** (Table II). Treatment of **37** with (*R,R*)-**1** in toluene at −78 °C provided a 73:27 mixture of **38**, with the desired syn relationship between methyl groups at C(24) and C(22), and its 22,24-anti diastereomer **39**. Diastereoselectivity in this mismatched double asymmetric reaction is lower than that of **11** described previously (Table II), since the intrinsic diastereofacial selectivity of **37** is presumably greater than that of **11**. Although a synthesis of the rifamycin S ansa chain certainly could have been completed via **38**, we turned instead to an alternative set of bond disconnections that led to a more highly stereoselective synthesis.



A revised set of bond disconnections are indicated in the new subtarget **40**. The troublesome syn relationship between the C(22) and C(24) methyl groups would be established in the first C–C bond forming step by using the mismatched double asymmetric reaction of (*S*)-**11b** and (*S,S*)-**1** (Table II, entry 6) that provides **13b** with 90% stereoselectivity (70–75% isolated yield of **13b**). From this point, the C(20)–C(21) bond (B′) would be assembled by a matched double asymmetric reaction with (*R,R*)-**1**, and then the direction of chain growth would be reversed to allow the bond C and D constructions to proceed as previously described.



Order of Bond Constructions:
Bond A - Matched, (S,S)-**2**
Bond B - Mismatched, (R,R)-**1**
Bond C - Matched, (S,S)-**1**
Bond D - Matched, (R,R)-**16**

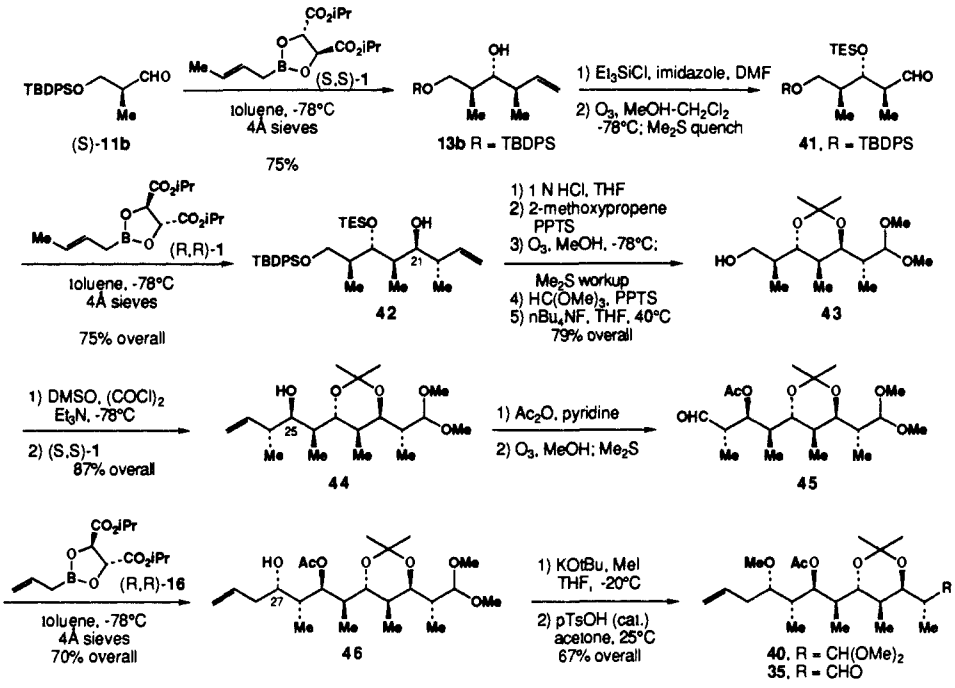


Order of Bond Constructions:
Bond A' - Mismatched, (S,S)-**1**
Bond B' - Matched, (R,R)-**1**
Bond C - Matched, (S,S)-**1**
Bond D - Matched, (R,R)-**16**

(21) (a) Rinehart, K. L., Jr.; Shield, L. S. In *Progress in the Chemistry of Organic Natural Products*; Hertz, W., Grisebach, H., Kirby, G. M., Eds.; Springer-Verlag: New York, 1976; Vol. 33, p 231. (b) Wehrli, W. *Top. Curr. Chem.* **1977**, *72*, 22. (c) Brufani, M. *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Wiley: New York, 1977; Vol. 1, p 91.

(22) (a) A total synthesis of rifamycin S was reported by Kishi and coworkers in 1980: Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. Iio, H.; Nagaoka, H.; Kishi, Y. *Ibid.* **1980**, *102*, 7965. (b) For other efforts directed toward the synthesis of the ansa chain, see: (c) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335. (d) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749. (e) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (f) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528. (g) Nakata, M.; Enari, H.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3283. (h) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (i) Fraser-Reid, B.; Magdzinski, L.; Molino, B. *Ibid.* **1984**, *106*, 731. (j) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289. (k) Rama Rao, A. V.; Yadav, J. S.; Vidyasagar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 55. (l) Tschamber, T.; Waespe-Šarčevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621. (m) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862. (n) Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5442. (o) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293.

Scheme III

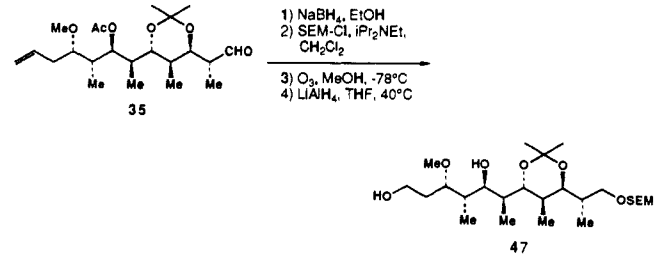


Thus, **13b** was converted to aldehyde **41** that was used directly without purification in a crotylboration with (*R,R*)-**1**. This reaction was exceptionally selective and provided **42** in 76% yield overall from **13b** (Scheme III). The diastereoselectivity was 98% as determined by HPLC analysis, and the minor product was determined to be the C(21)–hydroxyl epimer of **42** by an independent synthesis from **41** and (*S,S*)-**2**. Since (*R,R*)-**1** used in this crotylboration was only ca. 96% isomerically pure (prepared by the $FB(OMe)_2$ route),[3] it is probable that the 2% diastereomeric impurity derives from the contaminating (*Z*)-crotylboronate present in **1**.

The functionality at the two ends of **42** was adjusted to permit chain elongation from C(25). The TES ether was smoothly hydrolyzed by exposure to 1 N HCl in THF, then an acetonide was introduced between the C(21) and C(23) hydroxyl groups by treatment of the diol with pyridinium *p*-toluenesulfonate (PPTS) and excess 2-methoxypropene. Next, the vinyl appendage was subjected to a standard ozonolysis reaction, and the resulting aldehyde was protected as a dimethyl acetal (trimethyl orthoformate, PPTS). Finally, the TBDPS ether was cleaved by treatment with Bu_4NF in THF to give alcohol **43**. The overall yield of **43** for this five-step sequence was 79%.

Oxidation of **43** by using a standard Swern procedure[23] provided the corresponding aldehyde that was treated with (*S,S*)-**1**. This third crotylboration proved, as expected, to be a matched double asymmetric reaction and provided a 95:5 mixture of **44** and the C(25) epimer (HPLC analysis). The minor diastereomer in this reaction, as was also the case in the crotylboration of **41**, derives from contaminating (*Z*)-crotylboronate in the ca. 96% isomerically **1** used in these experiments. This underscores the importance of using **1** with very high isomeric purity.[3]

We now faced a critical tactical issue. Should the C(25) hydroxyl group of **44**, destined to become the acetoxy group of **35**, be protected to facilitate C(27)–C(28) bond construction? We reasoned that if the potentially sensitive β-acetoxy aldehyde **45** could be prepared, the subsequent reaction with (*R,R*)-**16** would proceed smoothly owing to the neutrality, high reactivity, and chemospecificity of the tartrate ester modified allylboronates. Indeed, acylation of **44** followed by ozonolysis in MeOH (−78 °C; Me_2S quench) provided crude **45** which was immediately treated with (*R,R*)-**16** under standard conditions. This reaction provided a 91:9 mixture of **46** and the C(27) epimer, from which **46** was isolated in 71% yield.[24] The requisite methyl ether was then prepared by treatment of a THF solution of **46** and excess CH_3I (−20 °C) with KO-*t*-Bu. Under these conditions an easily separated 8:1 mixture of **40** and the regioisomer resulting from acyl transfer prior to methylation was obtained (70% yield of **40**). Thus, protecting group chemistry was not required during the conversion of **44** to **40**. Finally, deprotection of **40** by exposure to catalytic *p*-TsOH in acetone led uneventfully to **35** (67% from **46**). The stereochemistry of **35** was verified by correlation with a reference sample of naturally derived **47** that was kindly provided by Professor Masamune.[25] The two samples were indistinguishable by ^1H NMR (250 MHz), ^{13}C NMR (100 MHz), IR, $[\alpha]_D$, and TLC analysis in three solvent systems, thereby confirming the stereostructure of **35** to be as shown.



Summary

This synthesis of the C(19)–C(29) segment **35** of the rifamycin S ansa chain provides clear testimony to the potential of the tartrate crotyl- and allylboronates as reagents for organic synthesis. This synthesis proceeds by a 16-step sequence from aldehyde **11b** and is both efficient (15% overall) and highly stereoselective (76% overall). More importantly, an empirical model has emerged through this synthesis and our investigations of the double asymmetric reactions of **11** and **20**, summarized in Tables II, III, and V, that enables one to predict high selectivity applications of this technology in organic synthesis. According to this model, dipropionate substructures **7** and **9** with anti relationships between branching methyl groups can be prepared with very high selectivity

(23) Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(24) The 4,5-syn diastereomer is intrinsically favored (Felkin) in the reactions of α-methyl chiral aldehydes and achiral allylboronates (ref 4c, 14). Thus, the combination of **45** and (*R,R*)-**16** is a matched pair. When (*S,S*)-**16** was employed, **46** and its C(27) epimer were obtained in ratio of 35:65.

(25) Full spectroscopic data for **47** are provided in the Supplementary Material to ref 22f as well as in the Ph.D. Thesis of B. Imperiali, Massachusetts Istitute of Technology, 1983.

via matched double asymmetric reactions, while substructures **8** and **10** with syn relationships between methyl branches are more difficult to prepare via mismatched double asymmetric reactions. Moreover, the ease of preparation of **7** and **9**, and the difficulty of achieving access to **8** and **10**, are expected to increase as the intrinsic diastereofacial preference of the chiral aldehyde substrate increases.

A number of comparably selective chiral crotylmetal reagents have appeared in the literature with absolute claims of superiority due to enantioselectivity or diastereoselectivity studies with relatively simple substrates.[10] While it is clear that, on average, the tartrate crotylboronates **1** and **2** are somewhat less enantioselective than the other "high selectivity" chiral crotylboron reagents that have emerged,[10] we believe that **1** and **2** are clearly the reagents of choice for the synthesis of the matched dipropionate substructures **7** and **9**. Each of the available chiral crotylboron reagents should provide **7** and **9** with comparably excellent, but not necessarily perfect stereocontrol, consequently the balance tips in favor of **1** and **2** owing to their ease of preparation and stability to storage: these criteria are unmatched by any of the competitive chiral crotylboron reagents.[10]

Synthesis of the mismatched dipropionate substructure **8** remains the most significant challenge in this area of acyclic diastereoselection. Substructure **10** poses relatively fewer problems since it can be prepared with very high diastereoselectivity by using Type II crotylstannane chemistry[13a,16] and/or via asymmetric aldol technology.[7] Of the chiral allylmetal reagents reported to date, the one that is most effective for the synthesis of substructure **8**, particularly in the most demanding cases of mismatched double diastereoselection, is the α-methoxy-(*E*)-crotylboronate developed by Hoffmann.[10e,g] Room remains for improvement, however, particularly with respect to the design of a chiral reagent that is more economical and synthetically accessible. Our continued efforts along these lines will be reported in due course.

Experimental Section

General. Proton (^{1}H) NMR spectra were recorded on either a Varian XL300 (300 MHz) or a Bruker WM 250-MHz spectrometer. Chemical shifts are reported in δ units with the 7.26 ppm resonance of residual chloroform as internal reference. Infrared spectra were recorded on a Perkin-Elmer Model 1420 infrared spectrophotometer. Melting points were measured on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1-mL capacity quartz cell (10-cm path length). Mass spectra were recorded on a KRATOS GC/MS 80 RFA Mass Spectrometer at the Indiana University Mass Spectroscopy Laboratory. Elemental analyses were performed by either Robertson Laboratories, Florham Park, NJ, or Galbraith Laboratories, Inc., Knoxville, TN. Unless otherwise noted, all compounds purified chromatographically are sufficiently pure (≥95% by ^{1}H NMR analysis) for use directly in subsequent preparative reactions.

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

Analytical thin-layer chromatography (TLC) was performed by using 2.5 × 10 cm plates coated with 0.25-mm thickness of F_{254} silica gel (E. M. Science). Preparative thin-layer chromatography was performed by using 20 cm × 20 cm plates coated with 0.25- or 0.50-mm thicknesses of F_{25}4 silica gel (E. M. Science). Flash chromatography was performed by using Kieselgel 60 (70 – 230 mesh, E. M. Science). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4 or phosphomolybdic acid. Analytical HPLC was performed by using a Waters Model 6000A solvent delivery system equipped with a 4.6 × 250 mm ChemcoPak column packed with 3 μ Chemcosorb silica gel. Compounds were detected by using either a Waters Model 440 Absorbance Detector operating at 254 nm or a Waters Series R401 Differential Refractometer. HPLC solvents (EtOAc, hexane) were degassed prior to use.

(*S*)-2-Methyl-3-[(*tert*-butyldiphenylsilyl)oxy]propanal (11b). To a solution of oxalyl chloride (10.2 mL, 127 mmol) in 200 mL of anhydrous CH_2Cl_2 under Ar at −78 °C was added DMSO (11.9 mL, 170 mmol) carefully via syringe (vigorous gas evolution) over a 15-min period. The resulting mixture was stirred for 30 min, and then a solution of 18.5 g (56.5 mmol) of (*R*)-2-methyl-3-[(*tert*-butyldiphenylsilyl)oxy]propan-1-ol (deriving from methyl-(*S*)-2-methyl-3-hydroxypropionate)[12a] in 50 mL of dry CH_2Cl_2 was introduced dropwise via cannula over a 15-min period. whereupon the reaction mixture turned cloudy white. The resulting mixture was stirred for an additional 20 min and then treated with triethylamine (38.1 mL, 254 mmol), added rapidly via syringe. The cooling bath was removed and the reaction allowed to warm gradually to room temperature. After 15 min at room temperature, the reaction was judged complete by TLC analysis and then was quenched by distributing the heterogeneous mixture between pentane and brine (250 mL each). The aqueous layer was separated and extracted with pentane (3 × 100 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate under reduced pressure yielded crude aldehyde **11b** as a yellow liquid that was contaminated with residual Et_3N·HCl. This material was combined with a second batch of **11b** (56.5-mmol scale oxidation) and used in the following reaction without further purification.

Aldehydes **11a** and **11c** were similarly prepared,[12] albeit on a smaller scale, for use in the diastereoselective crotylborations described in Table II.

Procedure for the Reactions of 1 and 2 with Aldehydes 11a–c. Preparation of (2*S*,3*S*,4*R*)-2,4-Dimethyl-1-[(*tert*-butyldiphenylsilyl)oxy]-hex-5-en-3-ol (13b). To a slurry of 2 g of 4-Å powdered molecular sieves in 100 mL of anhydrous toluene under Ar at room temperature was added (*S*,*S*)-**1** (170 mL, 170 mmol, 1.0 M solution in toluene, 99% isomeric purity).[3] After being stirred for 10 min at room temperature, the mixture was cooled to −78 °C. A solution of aldehyde **11b** (crude, theoretically 113 mmol) in 100 mL of dry toluene was then introduced dropwise via cannula over a 2-h period. After the addition was complete, the solution was maintained at −78 °C for 10 h. Excess ethanolic $NaBH_4$ (~0.75 g in 10 mL of absolute EtOH) was then added dropwise via pipet, the cooling bath was removed and the solution warmed to 0 °C. The mixture was then diluted with 300 mL of 1 N NaOH and stirred vigorously for 2 h. The layers were then separated and the aqueous layer was extracted with Et_2O (5 × 300 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated to a thick yellow liquid. HPLC analysis revealed that only **13b** and **12b** were present in a 90:10 ratio (5% EtOAc–hexane, flow rate of 0.7 mL/min, UV detection; retention times: **12b**, 9.2; **13b**, 7.4; **14b**, 8.0; **15b**, 9.8 min). The crude product was chromatographed (flash SiO_2, 9:1 hexane–Et_2O, 90 × 200 mm column) to provide initially 18.8 g of pure **13b**, 6.58 g of a 95:5 mixture of **13b**:**12b**, and 7.10 g of a 50:50 mixture of **13b**:**12b**. The combined yield is 32.5 g (77% overall from the alcohol precursor to **11b**), and the mixed fractions are easily separated to provide additional quantities of pure **13b**.

All other experiments summarized in Table II were performed typically by using 0.25-0.50 mmol of aldehyde, 1.5 equiv of either **1** or **2**, and 50 mg of 4-Å molecular sieves in 1–2 mL of toluene (~0.2 M final concentration). These reactions were run for 4 h at −78 °C. The crude reaction mixtures were analyzed by HPLC to determine diastereomeric product ratios.

HPLC for 12a–15a: 5% EtOAc–hexane, flow rate of 0.7 mL/min, refractive index detection; retention times: **12a**, 8.0; **13a**, 6.2; **14a**, 6.7; **15a**, 8.9 min.

HPLC for 12c–15c: 10% EtOAc–hexane, flow rate of 1.1 mL/min, UV detection; retention times: **12c**, 9.5; **13c**, 7.8; **14c**, 8.5; **15c**, 10.2 min.

Stereochemical assignments for **12b,c**, **13b,c**, **14b,c**, and **15a–c** are based on ^{1}H NMR comparisons with the spectral data for authentic samples provided by Keck.[13a] The stereochemical assignments of **12a**, **13a**, and **14a** are based on mechanistic considerations and the similarities of their ^{1}H NMR spectra with stereocongeners in the TBDPS and benzyl ether protected series.

Data for **12a**: $[\alpha]^{20}_D$ −3.9° (*c* 2.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 [ddd, *J* = 14.6, 9.3, 8.6 Hz, 1 H], 5.13–5.06 [m, 2 H], 3.72–3.66 [m, 2 H], 3.53 [dd, *J* = 8.3, 1.8 Hz, 1 H], 2.79 [bs, 1 H], 2.26 [m, 1 H], 1.79 [m, 1 H], 0.94 [d, *J* = 6.6 Hz, 3 H], 0.93 [d, *J* = 7.3 Hz, 3 H], 0.89 [s, 9 H], 0.06 [s, 6 H]; IR (neat) 3600–3400 (br), 3080, 2960, 2930, 2860, 1640, 1470, 1460, 1390, 1360, 1255, 1095, 1005, 980, 910, 835, 775 cm^{-1}.

Data for **13a**: $[\alpha]^{20}_D$ +17.0° (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 [ddd, *J* = 16.5, 10.0, 8.5 Hz, 1 H], 5.07–5.02 [m, 2 H], 3.82 [bs, 1 H], 3.74 [dd, *J* = 9.7, 3.7 Hz, 1 H], 3.61 [dd, *J* = 10.6, 7.5 Hz, 1 H], 3.37 [m, 1 H], 2.35 [m, 1 H], 1.77 [m, 1 H], 1.10 [d, *J* = 7.5 Hz, 3 H], 0.90 [s, 9 H], 0.82 [d, *J* = 6.7 Hz, 3 H], 0.07 [s, 6 H]; IR (neat) 3600–3400 (br), 3080, 2960, 2930, 2860, 1640, 1470, 1460, 1390, 1360, 1255, 1075, 1005, 910, 835, 775 cm^{-1}.

Data for **14a**: $[\alpha]^{20}_D$ +9.1° (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 [ddd, *J* = 15.7, 9.9, 7.3 Hz, 1 H], 5.06–4.99 [m, 2 H], 3.83 [dd, *J* = 10.2, 4.7 Hz, 1 H], 3.60–3.56 [m, 2 H], 3.39 [m, 1 H], 2.32 [m, 1 H], 1.78 [m, 1 H], 1.04 [d, *J* = 6.6 Hz, 3 H], 0.89 [d, *J* = 7.0 Hz, 3 H], 0.88 [s, 9 H], 0.06 [s, 6 H]; IR (neat) 3510 (br), 3080, 2960, 2930, 2860, 1640, 1470, 1460, 1390, 1360, 1205, 1075, 1005, 995, 910, 860, 835, 775 cm^{-1}.

Data for **15a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 [ddd, J = 17.2, 10.2, 8.5 Hz, 1 H], 5.08–4.94 [m, 2 H], 3.77 [dd, J = 9.8, 3.5 Hz, 1 H], 3.66 [dd, J = 9.8, 4.2 Hz, 1 H], 3.56 [dd, J = 9.1, 2.1 Hz, 1 H], 3.24 [bs, 1 H], 2.29 [m, 1 H], 1.76 [m, 1 H], 1.10 [d, J = 6.6 Hz, 3 H], 0.94 [d, J = 7.0 Hz. 3 H], 0.90 [s, 9 H], 0.07 [s, 6 H]; IR (neat) 3600–3400 (br), 2960, 2930, 2860. 1470, 1460. 1390, 1360, 1205, 1075, 1005, 910, 860, 835, 775 cm^{-1}.

Data for **12b**: $[\alpha]^{20}_D$ +4.9° (c 2.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.64 [m, 4 H], 7.44–7.35 [m, 6 H], 5.83 [ddd, J = 17.7, 9.4, 8.2 Hz, 1 H], 5.13–5.07 [m, 2 H], 3.71 [d, J = 5.7 Hz, 2 H], 3.57 [dd, J = 8.5. 3.0 Hz, 1 H], 2.42 [bs, 1 H], 2.27 [m, 1 H], 1.82 [m, 1 H], 1.04 [s, 9 H], 0.93 [d, J = 6.5 Hz, 6 H, overlapping methyls]; IR (neat) 3580, 3510 (br), 3070, 3050, 2960, 2930, 2860, 1640, 1590, 1470, 1460, 1430, 1390, 1360, 1110, 995, 915, 825, 740, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_2Si$: C, 75.39: H, 8.90. Found: C, 75.61: H, 9.00.

Data for **13b**: $[\alpha]^{20}_D$ +26.2° (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.66 [m, 4 H], 7.45–7.37 [m, 6 H], 5.93 [ddd. J = 16.9, 10.8, 8.4 Hz, 1 H], 5.08–5.03 [m, 2 H], 3.72 [dd, J = 10.1, 4.3 Hz, 1 H], 3.66 [dd, J = 10.5, 7.0 Hz, 1 H], 3.49 [bd, J = 3.0 Hz, 1 H], 3.43 [m, 1 H], 2.38 [m, 1 H], 1.84 [m, 1 H], 1.15 [d, J = 7.0 Hz, 3 H], 1.05 [s, 9 H], 0.80 [d, J = 6.9 Hz, 3 H]; IR (neat) 3500 (br), 3075, 3050, 2960, 2930, 2860, 1640, 1590, 1470, 1460, 1430, 1390, 1360, 1110, 1070, 995, 915, 825, 740, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_2Si$: C, 75.39; H, 8.90. Found: C, 75.10; H. 8.87.

Data for **14b**: $[\alpha]^{20}_D$ +2.3° (c 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.66 [m, 4 H], 7.46–7.37 [m, 6 H], 5.85 [ddd, J = 17.1, 9.6, 7.2 Hz, 1 H], 5.02–4.98 [m, 2 H], 3.82 [dd, J = 9.9, 4.8 Hz, 1 H], 3.64 [dd, J = 10.4, 6.1 Hz, 1 H], 3.49 [m, 1 H], 3.40 [d, J = 4.3 Hz, 1 H], 2.33 [m, 1 H], 1.83 [m, 1 H], 1.06 [d, J = 6.5 Hz, 3 H], 1.05 [s, 9 H], 0.90 [d, J = 6.6 Hz, 3 H]: IR (neat) 3510 (br), 3070, 3050, 2960, 2930, 2860, 1640, 1590, 1470, 1460, 1430, 1390, 1360, 1110, 1070, 995, 915, 825, 740, 700 cm^{-1}.

Data for **15b**: $[\alpha]^{20}_D$ +2.4° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.63 [m, 4 H], 7.45–7.36 [m, 6 H], 5.60 [ddd, J = 17.1, 10.0, 8.5 Hz, 1 H], 5.05–4.93 [m, 2 H], 3.75 [dd, J = 9.6, 3.7 Hz, 1 H], 3.66–3.61 [m, 2 H], 2.84 [bs, 1 H], 2.29 [m, 1 H], 1.79 [m, 1 H], 1.10 [d, J = 6.8 Hz, 3 H], 1.05 [s, 9 H], 0.95 [d, J = 6.5 Hz, 3 H]; IR (neat) 3520 (br). 3080, 3050, 2960, 2930, 2860, 1640, 1590, 1470, 1460, 1430, 1110, 1090, 995, 980, 915, 820, 740, 700 cm^{-1}.

Data for **12c**: $[\alpha]^{20}_D$ +11.9° (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 [m, 5 H], 5.79 [ddd, J = 17.1, 10.2, 8.7 Hz, 1 H], 5.15–5.07 [m, 2 H], 4.52 [s, 2 H], 3.56 [dd, J = 9.0, 6.0 Hz, 1 H], 3.55 [dd, J = 9.0, 6.2 Hz, 1 H], 3.45–3.42 [m, 2 H], 2.28–2.23 [m, 2 H], 1.97 [m, 1 H], 0.97 [d, J = 6.7 Hz, 3 H], 0.95 [d, J = 6.9 Hz, 3 H]; IR (neat) 3400 (br), 3060, 3030, 2970, 2930, 2880, 1640, 1455, 1275, 1100, 1060, 1000, 915, 750, 715, 700 cm^{-1}.

Data for **13c**: $[\alpha]^{20}_D$ +15.3° (c 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 [m, 5 H], 5.92 [ddd, J = 17.8, 8.9, 8.3 Hz, 1 H], 5.08–5.02 [m, 2 H], 4.51 [s, 2 H], 3.58 [dd, J = 9.1, 4.5 Hz, 1 H]. 3.53–3.47 [m, 1 H], 3.35 [m, 1 H], 2.35 [m, 1 H], 1.93 [m, 1 H], 1.09 [d, J = 6.9 Hz, 3 H], 0.88 [d, J = 6.9 Hz,3 H]; IR (neat) 3490 (br), 3070, 3030, 2960, 2930, 2870, 1635, 1455, 1090, 1070, 1000, 910, 735, 700 cm^{-1}.

Data for **14c**: $[\alpha]^{20}_D$ +2.9° (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz. $CDCl_3$) δ 7.37–7.27 [m, 5 H], 5.86 [ddd, J = 17.6, 9.7, 7.2 Hz, 1 H], 5.06–5.00 [m, 2 H], 4.51 [s, 2 H], 3.66 [dd, J = 9.1, 4.3 Hz, 1 H], 3.50 [dd, J = 9.1, 6.2 Hz, 1 H], 3.40 [m, 1 H], 3.16 [d, J = 4.3 Hz, 1 H], 2.31 [m, 1 H], 2.00 [m, 1 H], 1.04 [d, J = 6.7 Hz, 3 H], 0.96 [d, J = 7.0 Hz, 3 H]; IR (neat) 3490 (br), 3070, 3030, 2970, 2910, 2860, 1640, 1455, 1090, 1070, 995, 910, 725, 700 cm^{-1}.

Data for **15c**: $[\alpha]^{20}_D$ +6.4° (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 [m, 5 H], 5.63 [ddd, J = 17.2, 10.2, 8.6 Hz, 1 H], 5.09–4.95 [m, 2 H], 4.50 [br s, 2 H], 3.57–3.49 [m, 3 H], 2.62 [d, J = 2.9 Hz, 1 H], 1.98 [m, 1 H], 1.93 [m, 1 H], 1.09 [d, J = 6.6 Hz, 3 H], 0.96 [d, J = 6.9 Hz, 3 H]; IR (neat) 3490, 3070, 3030, 2960, 2930, 2870, 1630, 1490, 1365, 1205, 1095, 1025, 910, 725, 700 cm^{-1}.

(2*R*,4*S*)-2,4-Dimethyl-1-[(*tert*-butyldiphenylsilyl)oxy]hex-5-ene (19). To a solution of 1.17 g (3.0 mmol) of alcohol **13b** in 15 mL of anhydrous THF under Ar at −78 °C was added *n*-BuLi (2.29 mL, 3.66 mmol, 1.6 M in hexane) dropwise via syringe. The solution was stirred for 30 min at −78 °C, then *p*-TsCl (0.69 g, 3.6 mmol) was added in small portions. After 10 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Cold (0 °C) water (20 mL) was then added. After the mixture was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extracts were combined and washed successively with 30-mL portions of 0.5 N HCl, saturated $NaHCO_3$, and brine. The solution was dried (Na_2SO_4), filtered. and concentrated under reduced pressure to give 1.61 g (98% yield) of the crude tosylate as a pale yellow liquid. This intermediate was used in the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.58 [m, 6 H], 7.48–7.32 [m, 6 H], 7.18–7.11 [m, 2 H], 5.70 [ddd, J = 17.1, 11.0, 9.2 Hz, 1 H], 4.97–4.88 [m, 2 H], 4.62 [dd, J = 7.0, 3.5 Hz, 1 H], 3.56 [dd, J = 9.2, 4.8 Hz, 1 H]. 3.38 [dd, J = 9.2, 5.9 Hz, 1 H], 2.58 [m, 1 H], 2.35 [s, 3 H], 2.09 [m, 1 H], 1.06 [s, 9 H], 0.97 [d, J = 6.5 Hz, 3 H], 0.89 [d, J = 6.6 Hz, 3 H]; IR (neat) 3070, 3040, 2960, 2930, 2850, 1640, 1600, 1590, 1470, 1460, 1435, 1390, 1360, 1190, 1175, 1100, 995, 900, 840, 820, 810, 740, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{40}O_4SSi$: C, 69.36; H, 7.57. Found: C, 69.42; H, 7.63.

To a solution of the above tosylate (0.544 g, 1.00 mmol) in 10 mL of anhydrous THF under Ar at room temperature was added $LiAlH_4$ (0.114 g, 3.00 mmol). The resulting mixture was heated to reflux for 1.5 h. After being cooled to 0 °C, the reaction was treated with 10 mL of cold (0 °C) brine (added dropwise). After the mixture was stirred for 15 min, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The organic extracts were combined and dried ($MgSO_4$). Filtration and concentration under reduced pressure yielded a pale yellow oil that was chromatographed (flash SiO_2, hexane–CH_2Cl_2 50:1) to give 0.232 g (63%) of **19** as a colorless oil: $[\alpha]^{20}_D$ +4.8° (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.67 [m, 4 H], 7.47–7.36 [m, 6 H], 5.62 [ddd, J = 17.2, 11.0, 7.6 Hz, 1 H], 4.96 [dd, J = 17.2, 2.0 Hz, 1 H], 4.92 [dd, J = 11.0, 2.0 Hz, 1 H], 3.53–3.41 [m, 2 H], 2.22 [m, 1 H], 1.74 [m, 1 H], 1.44 [ddd, J = 13.1, 8.4, 5.3 Hz, 1 H], 1.07 [s, 9 H], 1.04 [m, 1 H, partially obscured by ^{t}Bu and methyl groups], 0.98 [d, J = 7.3 Hz, 3 H], 0.92 [d, J = 6.6 Hz, 3 H]; IR (neat) 3080, 3050, 2960, 2920, 1640, 1425, 1380, 1110, 910, 820, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{34}OSi$: C, 78.63; H, 9.35. Found: C, 78.54; H, 9.59.

Ozonolysis of 19 and the Crotyl- and Allylboration of 20. A solution of **19** (78 mg, 0.21 mmol) in 3 mL of a 1:1 mixture of anhydrous CH_2Cl_2 and MeOH at −78 °C was treated with a stream of ozone until the solution turned blue. Excess ozone was then removed by passing a stream of N_2 through the solution until the color was discharged. After the reaction was warmed to room temperature, 0.2 mL of Me_2S were added. The solution was stirred for 2 h, and then the excess Me_2S and solvent were removed under reduced pressure to provide the crude aldehyde **20** as a colorless oil. The aldehyde was dissolved in 1.0 mL of anhydrous toluene and used immediately in the next reaction without further purification.

The crotyl- and allylborations of **20** were performed as described for **11a–c** with the exception that the experiments summarized in Table V were performed at −85 to −95 °C. As before, the crude reaction mixtures were analyzed by HPLC to determine diastereomeric product ratios.

HPLC for 21–26: 4% EtOAc–hexane, flow rate of 1.0 mL/min, UV detection; retention times: **21**, 11.1; **22**, 11.1; **23**, 15.0; **24**, 17.0; 25. 21.3; **26**, 23.2 min. Isomers **21** and **22** could not be resolved by HPLC, and the relative amounts of these diastereomers were determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture.

Data for **21**: $[\alpha]^{20}_D$ +2.7° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 [m, 4 H], 7.45–7.33 [m, 6 H], 5.71 [ddd, J = 17.0, 9.8, 8.2 Hz, 1 H], 5.18–5.09 [m, 2 H], 3.57 [dd, J = 9.1. 4.2 Hz, 1 H], 3.45 [dd, J = 9.1, 5.8 Hz, 1 H], 3.15 [m, 1 H], 2.28 [m, 1 H], 1.81–1.68 [m, 2 H], 1.57–1.48 [m, 2 H], 1.08 [m, 1 H], 1.06 [s, 9 H], 0.97 [d, J = 6.8 Hz, 3 H], 0.92 [d, J = 6.8 Hz, 3 H], 0.85 [d, J = 7.0 Hz, 3 H]; IR (neat) 3490 (br), 3075, 3050, 2960, 2920, 2850, 1635, 1425, 1390, 1310, 1110, 1005, 995, 980, 915, 820, 795, 740, 700 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O_2Si$: C, 76.36; H, 9.49. Found: C, 76.12; H, 9.69.

Data for **22** (data obtained on a ~5:1 mixture of **22**:**21**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.67 [m, 4 H], 7.47–7.36 [m, 6 H], 5.75 [ddd, J = 17.5, 11.2, 9.3 Hz, 1 H], 5.13–5.07 [m, 2 H], 3.55 [dd, J = 9.8, 4.7 Hz, 1 H], 3.44 [dd, J = 9.8, 5.7 Hz, 1 H], 3.10 [m, 1 H], 2.37 [m, 1 H], 1.80–1.62 [m, 3 H], 1.47 [d, J = 4.5 Hz, 1 H], 1.07 [s, 9 H], 1.00 [d, J = 6.0 Hz, 3 H], 0.99 [d, J = 6.5 Hz, 3 H], 0.92 [d, J = 6.6 Hz, 3 H]; IR (neat) 3490 (br) 3075, 3050, 2960, 2920, 2850, 1635, 1425, 1390, 1310, 1110, 1005, 995, 980, 915, 820, 740, 700 cm^{-1}.

Data for **23**: $[\alpha]^{20}_D$ −23.7° (c 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.68 [m, 4 H], 7.49–7.35 [m, 6 H], 5.77 [ddd, J = 17.0, 10.1, 9.2 Hz, 1 H], 5.01 [dd, J = 17.0, 2.0 Hz, 1 H], 4.99 [dd, J = 10.1, 2.0 Hz, 1 H], 3.59 [dd, J = 9.1, 3.0 Hz, 1 H], 3.38 [dd, J = 9.1, 5.0 Hz, 1 H], 3.18 [m, 1 H], 2.38 [m, 1 H], 1.83–1.55 [m, 3 H], 1.36 [d, J = 3.0 Hz, 1 H], 1.08 [s, 9 H], 0.98 [d, J = 6.6 Hz, 3 H], 0.94 [d, J = 6.8 Hz, 3 H], 0.91 [m, 1 H], 0.87 [d, J = 7.0 Hz, 3 H]; IR (neat) 3480 (br), 3070, 2960, 2930, 2850, 1640, 1425, 1110, 1080, 1005, 995, 910, 820, 790, 740, 700 cm^{-1}; high-resolution mass spectrum (CI) for $C_{27}H_{41}O_2Si$ (M^+ + 1), calcd 425.2876; found 425.2835. Anal. Calcd for $C_{27}H_{40}O_2Si$: C, 76.36; H, 9.49. Found: C, 76.13; H, 9.68.

Data for **24**: $[\alpha]^{20}_D$ −5.2° (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 [m, 4 H], 7.46–7.35 [m, 6 H], 5.64 [ddd, J = 17.1, 9.1, 8.2 Hz, 1 H], 5.05 [dd, J = 17.2, 2.0 Hz, 1 H], 4.99 [dd, J = 9.1, 2.0 Hz, 1 H], 3.53–3.42 [m, 2 H], 3.21 [m, 1 H], 2.34 [m, 1 H], 1.76–1.68 [m, 2 H], 1.53–1.46 [m. 1 H], 1.30 [m, 1 H], 1.07 [d, J = 6.6

Hz, 3 H], 1.06 [s, 9 H], 1.00 [m, 1 H], 0.94 [d, J = 6.6 Hz, 3 H], 0.84 [d, J = 6.6 Hz, 3 H]; IR (neat) 3470 (br), 3060, 2960, 2920, 2850, 1640, 1425, 1390, 1110, 1080, 995, 960, 910, 820, 790, 740, 700, 695, 610 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O_2Si$: C, 76.36; H, 9.49. Found: C, 76.52; H, 9.66.

Data for **25**: $[\alpha]^{20}_D$ −2.0° (c 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69–7.66 [m. 4 H], 7.47–7.37 [m, 6 H], 5.81 [m, 1 H], 5.16–5.10 [m, 2 H], 3.57–3.42 [m, 3 H], 2.24–2.17 [m, 2 H], 1.78 [m, 1 H], 1.55–1.51 [m, 2 H], 1.43 [d, J = 3.9 Hz, 1 H], 1.08 [s, 9 H], 1.03 [m, 1 H], 0.98 [d, J = 6.5 Hz, 3 H], 0.86 [d, J = 6.6 Hz, 3 H]; IR (neat) 3450 (br), 3060, 3040, 2960, 2920. 2850, 1640, 1425, 1110, 980, 910, 820, 790, 740, 700 cm^{-1}. Anal. Calcd for $C_{26}H_{38}O_2Si$: C, 76.04; H, 9.33. Found: C. 75.83; H, 9.53.

Data for **26**: $[\alpha]^{20}_D$ −3.8° (c 2.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.62 [m, 4 H], 7.46–7.34 [m, 6 H], 5.83 [m, 1 H], 5.15–5.10 [m, 2 H], 3.56–3.40 [m, 3 H], 2.27 [m, 1 H], 2.08 [m, 1 H], 1.71 [m, 1 H], 1.62–1.50 [m, 4 H], 1.07 [s, 9 H], 0.98 [d, J = 6.7 Hz, 3 H], 0.86 [d, J = 6.6 Hz, 3 H]; IR (neat) 3400 (br), 3070, 2960, 2930, 2850, 1640, 1425, 1110. 1080, 995, 910, 820, 790, 740, 700 cm^{-1}. Anal. Calcd for $C_{26}H_{38}O_2Si$: C, 76.04; H, 9.33. Found: C, 75.99; H, 9.54.

(2*R*,4*S*,5*S*,6*S*)-5-Hydroxy-2,3,6-trimethyloct-7-enoic Acid δ-Lactone (27). To a solution of 98 mg (0.21 mmol) of alcohol **23** in 4 mL of anhydrous THF under Ar at room temperature was added n-Bu_4NF (0.63 mL, 0.63 mmol, 1.0 M in THF) via syringe. After 2 h, the reaction was poured into 5 mL of saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). Drying (Na_2SO_4), followed by concentration under reduced pressure gave a yellow oil that was chromatographed (flash SiO_2, hexane–Et_2O 1:1) to provide 46 mg (82%) of the corresponding diol as a thick colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 [ddd, J = 17.0, 11.2, 9.8 Hz, 1 H], 5.13–5.09 [m. 2 H], 4.57–4.45 [m, 2 H], 3.24 [dd, J = 8.7, 4.1 Hz, 1 H], 2.43 [m, 1 H], 2.30 [m, 1 H], 2.21 [bs, 2 H], 1.76–1.61 [m, 3 H], 1.02 [d, J = 6.5 Hz, 3 H], 0.98 [d, J = 6.8 Hz, 3 H], 0.91 [d, J = 6.6 Hz, 3 H].

To a solution of 17 mg (0.076 mmol) of the above diol in 10 mL of anhydrous benzene was added 550 mg (0.954 mmol) of freshly prepared Ag_2CO_3 on Celite. The resulting suspension was heated to reflux for 6 h. Upon cooling, the solids were filtered, and the filtrate was concentrated under reduced pressure to give an oily residue. Chromatography (flash SiO_2, hexane–Et_2O 3:1) yielded 13 mg (72%) of lactone **27**[19] as a colorless oil: $[\alpha]^{20}_D$ +37.5° (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 [ddd. J = 17.2, 10.1, 7.2 Hz, 1 H], 5.10 [dd, J = 17.2, 2.0 Hz, 1 H], 5.07 [dd, J = 10.1, 2.0 Hz, 1 H], 3.99 [dd, J = 10.4, 3.0 Hz, 1 H], 2.54–2.46 [m, 2 H], 1.98–1.90 [m, 2 H], 1.29 [d, J = 7.0 Hz, 3 H], 1.05 [d, J = 7.1 Hz, 3 H], 1.02 [d, J = 6.2 Hz, 3 H]; IR (neat) 2960, 2920. 1730, 1460, 1370, 1110, 995, 915 cm^{-1}; high-resolution mass spectrum (Cl) for $C_{11}H_{19}O_2$ (M^+ + 1), calcd 183.1385; found 183.1387.

(2*S*,3*S*,4*R*,5*S*,6*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3-[(triethylsilyl)oxy]-2,4,6-trimethyloct-7-ene (42). A solution of alcohol **13b** (7.00 g, 18.3 mmol) in 40 mL of dry DMF under Ar at 0 °C was treated with imidazole (2.74 g, 40.0 mmol) and triethylchlorosilane (3.70 mL, 22.0 mmol). After being vigorously stirred for 3 h, the reaction mixture was distributed between 1:1 hexane–Et_2O (150 mL) and brine (150 mL). The aqueous phase was then extracted with 1:1 hexane–Et_2O (2 × 100 mL). The organic extracts were combined and dried ($MgSO_4$). Concentration under reduced pressure gave a pale yellow oil that was chromatographed (flash SiO_2, hexane–Et_2O 5:1) to yield 8.98 g (98%) of the bissilyl ether as a free flowing liquid: $[\alpha]^{25}_D$ +11.1° (c 1.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.66–7.64 [m, 4 H], 7.40–7.31 [m, 6 H], 5.83 [ddd, J = 16.6, 10.3, 8.1 Hz, 1 H], 4.90 [m, 2 H], 3.73 [dd, J = 9.8, 5.4 Hz, 1 H], 3.50–3.39 [m, 2 H], 2.31 [m, 1 H], 1.85 [m, 1 H], 1.04 [s, 9 H], 0.95 [d, J = 7.0 Hz, 3 H], 0.89–0.82 [m, 12 H], 0.60–0.42 [m, 6 H]; IR (neat) 3070, 2980, 2880, 1470, 1460, 1430, 1390, 1360, 1240, 1110, 1045, 1005, 910, 820, 740, 700, 615 cm^{-1}; high-resolution mass spectrum (EI) for $C_{26}H_{39}O_2Si_2$ ($M^+ - C_4H_9$), calcd 439.2489; found 439.2491.

A −78 °C solution of the above bissilyl ether (3.97 g, 8.00 mmol) in 150 mL of 5:1 MeOH–CH_2Cl_2 was subjected to the standard ozonolysis procedure described for the preparation of **18**. The reaction was worked up by the addition of Me_2S (1.8 mL, 24 mmol). Excess Me_2S and solvent were then removed under reduced pressure to yield aldehyde **41** as a pale yellow liquid that was used in the next reaction without purification: ^1H NMR (250 MHz, $CDCl_3$) δ 9.74 [d, J = 2.4 Hz, 1 H], 7.64–7.63 [m, 4 H], 7.41–7.33 [m, 6 H], 4.01 [dd, J = 4.2, 4.2 Hz, 1 H], 3.65 [dd, J = 10.2, 6.9 Hz, 1 H], 3.49 [dd, J = 10.2, 6.5 Hz, 1 H], 2.54 [m, 1 H], 1.98 [m, 1 H], 1.07 [d, J = 7.5 Hz, 3 H], 1.04 [s, 9 H], 0.99–0.79 [m, 12 H], 0.68–0.42 [m, 6 H]; IR (neat) 3070, 3040, 2950, 2930, 2910, 2870, 2860, 1710, 1590, 1470, 1460, 1425, 1390, 1375, 1235, 1185, 1110, 1070, 1005, 970, 940, 820, 735. 700 cm^{-1}.

To a slurry of 0.5 g of powdered 4-Å molecular sieves in 25 mL of anhydrous toluene under Ar at room temperature was added (*R*,*R*)-**1** (8.42 mL, 16.0 mmol, 1.9 M in toluene) via syringe. The mixture was stirred for 5 min at 23 °C and then was cooled to −78 °C. A −78 °C solution of aldehyde **41** in 20 mL of anhydrous toluene was then introduced dropwise via cannula over a 1-h period. The resultant mixture was stirred for an additional 11 h at −78 °C and then was allowed to warm to room temperature. At this point 50 mL of 1 N NaOH was next added, and the heterogeneous mixture was stirred vigorously for 2 h. The layers were then separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give a thick oil. Chromatography of the crude product (flash SiO_2, hexane–ether 10:1) yielded 3.41 g (77%) of the desired alcohol **42** as a colorless oil. HPLC analysis (2% EtOAc–hexane, flow rate of 1.1 mL/min, retention time: **42**, 10.1; diastereomer **48**, 7.9 min; UV detection) of the crude reaction mixture showed that the major product was contaminated with ~2% of the C(21) hydroxyl epimer **48**, resulting from reaction of the (*Z*)-crotylboronate (present as a ca. 2% impurity in the (*R*,*R*)-**1** solution). An authentic sample of **48** was prepared by the crotylboration of **41** and (*S*,*S*)-(*Z*) crotylboronate **2**.

Data for **42**: $[\alpha]^{20}_D$ −2.3° (c 3.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.62 [m, 4 H], 7.42–7.32 [m, 6 H], 5.84 [ddd, J = 17.6, 9.9, 7.6 Hz, 1 H], 5.11–5.01 [m, 2 H], 3.74–3.64 [m, 3 H], 3.48 [s, 1 H], 3.45 [dd, J = 9.9, 7.2 Hz, 1 H], 2.21 [m, 1 H], 2.05 [m, 1 H], 1.83 [m, 1 H], 1.05 [s, 9 H], 0.96 [d, J = 7.0 Hz, 3 H], 0.91 [d, J = 6.9 Hz, 3 H], 0.87–0.81 [m, 12 H], 0.54–0.43 [m, 6 H]; IR (neat) 3580, 3500, 3070, 3050, 2960, 2870, 1640, 1590, 1460, 1450, 1445, 1430, 1425, 1390, 1310, 1240, 1110, 1005, 980, 940, 910, 825, 740, 700 cm^{-1}. Anal. Calcd for $C_{33}H_{54}O_3Si_2$: C, 71.42; H, 9.81. Found: C, 71.20; H, 9.77.

Data for the minor diastereomer **48** [the C(21) hydroxyl epimer of **42**] from the crotylboration of **41**: $[\alpha]^{20}_D$ +3.1° (c 3.30, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.62 [m, 4 H], 7.43–7.35 [m, 6 H], 5.96 [ddd, J = 16.7, 11.2, 9.5 Hz, 1 H], 5.07–5.00 [m, 2 H], 3.82 [dd, J = 4.8, 4.8, 1 H], 3.68 [dd, J = 10.2, 6.8 Hz, 1 H], 3.49–3.38 [m, 2 H], 3.33 [bs, 1 H], 2.29 [m, 1 H], 1.97 [m, 1 H], 1.76 [m, 1 H], 1.04 [s, 9 H], 0.95–0.86 [m, 15 H], 0.78 [d, J = 6.9 Hz, 3 H], 0.60–0.50 [m, 6 H]; IR (neat) 3520 (br), 3070, 3050, 2960, 2930, 2910, 2880, 2860, 1640, 1590, 1470, 1460, 1430, 1390, 1240, 1110, 1080, 1005, 970, 910, 840, 820, 800, 740, 700 cm^{-1}; high-resolution mass spectrum (EI) for $C_{29}H_{45}O_3Si_2$ ($M^+ - C_4H_9$), calcd 497.2937; found 497.2896.

(2*R*,3*S*,4*S*,5*S*,6*S*)-3,5-*O*-Isopropylidene-1,1-dimethoxy-2,4,6-trimethylheptane-3,5,7-triol (43). Alcohol **42** (3.20 g, 5.80 mmol) was dissolved in 50 mL of 3:2 1 N HCl/THF. The mixture was warmed to 45 °C and stirred vigorously for 1 h. The mixture was then cooled to room temperature and poured into 100 mL of cold (0 °C) saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the corresponding diol **49** as a thick colorless oil: $[\alpha]^{20}_D$ +17.2° (c 0.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.71–7.67 [m, 4 H], 7.45–7.36 [m, 6 H], 5.87 [ddd, J = 17.4, 9.9, 8.7 Hz, 1 H], 5.28–5.05 [m, 2 H], 4.64 [d, J = 2.9 Hz, 1 H], 3.78–3.61 [m, 5 H], 2.31 [m, 1 H], 2.04 [m, 1 H], 1.85 [m, 1 H], 1.07 [d, J = 6.6 Hz, 3 H], 1.02 [s, 9 H], 0.91 [d, J = 6.8 Hz, 3 H], 0.73 [d, J = 6.8 Hz, 3 H]; IR (neat) 3440 (br), 3070, 3050, 3010, 2960, 2930, 2860, 1640, 1590, 1490, 1470, 1460, 1430, 1390, 1235, 1135, 1105, 1110, 1070, 995, 970, 910, 820, 740, 700 cm^{-1}; high-resolution mass spectrum (EI) for $C_{23}H_{31}O_3Si$ ($M^+ - C_4H_9$), calcd 383.2042; found 383.2058.

The crude diol **49** was dried by coevaporation from two 30-mL portions of anhydrous THF. A solution of the diol in 50 mL of anhydrous Et_2O under Ar was then treated with 2-methoxypropene (2.4 mL, 29 mmol, 5 equiv) and a crystal of PPTS. After being stirred for 8 h at room temperature, the reaction was terminated by the addition of ~200 mg of solid K_2CO_3. After an additional 30 min, the reaction mixture was filtered through a pad of flash SiO_2 (hexane–Et_2O, 4:1) and concentrated under reduced pressure to give 2.55 g, (95%) of the corresponding acetonide **50** as a colorless oil. This material was used in the next reaction without further purification: $[\alpha]^{20}_D$ +18.2° (c 1.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.67–7.64 [m, 4 H], 7.42–7.33 [m, 6 H], 5.87 [ddd, J = 17.3, 10.4, 6.8 Hz, 1 H], 5.08–4.97 [m, 2 H], 3.67–3.62 [m, 2 H], 3.42–3.33 [m, 2 H], 2.23 [m, 1 H], 1.86–1.76 [m, 2 H], 1.27 [s, 3 H, acetonide methyl], 1.22 [s, 3 H, acetonide methyl], 1.02 [s, 9 H], 0.98 [d, J = 7.0 Hz, 3 H], 0.89–0.81 [m, 6 H]; IR (neat) 3070, 3050, 2960, 2930, 2860, 1640, 1470, 1430, 1380, 1225, 1180, 1110, 1020, 995, 910, 885, 820, 800, 740, 700 cm^{-1}. Anal. Calcd for $C_{30}H_{44}O_3Si$: C, 74.95; H, 9.22. Found: C, 74.96; H, 8.99.

A solution of 2.00 g (4.30 mmol) of the above acetonide **50** in 30 mL of anhydrous MeOH at −78 °C was subjected to the standard ozonolysis procedure described for **18**. The reaction was worked up by the addition of Me_2S (1.0 mL, 19.3 mmol). Excess Me_2S and solvent were removed

2 h later under reduced pressure to provide the crude aldehyde **51** as a thick, colorless oil. This material was used immediately in the next reaction without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.65 [d, J = 3.0 Hz, 1 H], 7.67–7.63 [m, 4 H], 7.41–7.32 [m, 6 H], 3.86 [dd, J = 10.9. 4.1 Hz, 1 H], 3.64 [d, J = 5.3 Hz, 2 H], 3.36 [dd, J = 6.5, 6.2 Hz, 1 H]. 2.43 [m, 1 H], 1.87–1.78 [m, 2 H], 1.26 [s, 3 H], 1.24 [s, 3 H], 1.03 [s, 9 H], 0.98 [d. J = 6.8 Hz, 3 H], 0.90 [d, J = 7.0 Hz, 3 H], 0.88 [d, J = 6.6 Hz. 3 H]; IR (neat) 3070, 3050, 2950, 2930, 2880, 2860, 2700, 1730. 1590, 1480, 1470. 1430, 1380, 1225, 1180, 1110, 995, 885, 825, 740, 700 cm^{-1}.

To a solution of the crude aldehyde **51** in 20 mL of anhydrous CH_2Cl_2 under Ar was added trimethyl orthoformate (9.4 mL, 86 mmol) along with 5 mg of PPTS. The resulting mixture was stirred for 5 h at room temperature before being quenched by the addition of 100 mg of solid K_2CO_3. The mixture was stirred for 15 min, and then the solid was filtered and the filtrate concentrated under reduced pressure to give a colorless oil. Chromatography (flash SiO_2, hexane–ether 4:1) provided 2.08 g (93% overall) of the dimethyl acetal **52** as a colorless oil: $[\alpha]^{25}_D$ +11.8° (c 2.65, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73–7.67 [m, 4 H], 7.45–7.36 [m, 6 H], 4.41 [d, J = 2.2 Hz, 1 H]. 3.70–3.65 [m, 3 H], 3.44 [s, 3 H], 3.42 [s, 3 H], 3.37 [dd, J = 6.4, 6.4 Hz, 1 H]. 1.84–1.74 [m, 2 H]. 1.28 [s, 3 H], 1.25 [s, 3 H], 1.03 [s, 9 H]. 0.98 [d, J = 6.7 Hz, 3 H], 0.84 [d, J = 6.7 Hz, 3 H], 0.76 [d, J = 6.8 Hz, 3 H]; IR (neat) 3070, 3050, 2980, 2960, 2930, 2880, 2860, 1470, 1460, 1430, 1380, 1225, 1190, 1150, 1110, 1070, 1020, 1000, 880, 820, 800, 740, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{48}O_5Si$: C, 70.35; H, 9.15. Found: C, 70.53; H, 8.93.

To a solution of 1.71 g (3.30 mmol) of dimethyl acetal **52** in 30 mL of anhydrous THF under Ar at room temperature was added n-Bu_4NF, (13.0 mL, 13.0 mmol, 1 M soln in THF). The resulting mixture was heated to 40 °C. After 1.5 h, the reaction mixture was allowed to cool to room temperature and then poured into 50 mL of saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O (3 × 40 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude alcohol as a yellow oil. Chromatography (flash SiO_2, hexane–Et_2O 3:1) then yielded 0.79 g (89%) of alcohol **43** as a colorless oil: $[\alpha]^{25}_D$ +21.4° (c 0.70, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.41 [d, J = 2.3 Hz, 1 H], 3.74 [dd, J = 10.8, 3.9 Hz, 1 H], 3.72–3.68 [m. 1 H], 3.60–3.50 [m, 1 H], 3.44 [s, 3 H], 3.42 [s, 3 H], 3.25 [dd, J = 6.4, 6.4 Hz, 1 H], 2.83 [br s, 1 H], 1.86–1.73 [m. 3 H], 1.33 [s, 3 H], 1.30 [s, 3 H], 0.97 [d, J = 7.0 Hz, 3 H], 0.86 [d, J = 6.7 Hz, 3 H], 0.80 [d, J = 6.8 Hz, 3 H]; IR ($CHCl_3$) 3450 (br), 2980, 2930, 2880, 2830, 1460, 1380, 1225, 1190, 1150, 1105, 1070, 1020, 995, 975, 950, 925, 905, 880 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_5$: C, 62.04; H, 10.41. Found: C, 61.98; H, 10.32.

(2*R*.3*R*.4*S*.5*S*.6*S*.7*R*.8*R*)-3.5-*O*-Isopropylidene-1.1-dimethoxy-2.4.6.8-tetramethyldec-9-ene-3.5.7-triol (44). To a solution of oxalyl chloride (0.41 mL, 5.10 mmol) in 10 mL of anhydrous CH_2Cl_2 under Ar at −78 °C was added DMSO (0.57 mL, 8.2 mmol) dropwise via syringe. This mixture was stirred for 10 min and then a −78 °C solution of alcohol **43** (593 mg, 2.04 mmol) in 5 mL of CH_2Cl_2 was added dropwise via cannula over a 5-min period. After an additional 15 min at −78 °C, Et_3N (1.53 mL, 10.2 mmol) was added slowly via syringe. The resultant heterogeneous mixture was allowed to gradually warm to room temperature. After 15 min, the reaction was distributed between 10 mL of CH_2Cl_2 and 30 mL of brine. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The organic was dried by passing the solution through a cotton plug. Concentration under reduced pressure gave a pale yellow oil that was triturated with cold Et_2O. The solid Et_3N·HCl was filtered off, and the solution was concentrated under reduced pressure to a pale yellow oil. The resulting crude aldehyde **53** was used immediately in the next reaction without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.71 [d, J = 2.6 Hz, 1 H], 4.40 [d, J = 2.4 Hz, 1 H], 3.73 [dd, J = 10.9, 4.2 Hz, 1 H], 3.43 [s, 3 H], 3.42 [dd, 1 H, masked by methoxyls], 3.41 [s, 3 H], 2.44 [m, 1 H], 1.95–1.76 [m, 2 H], 1.30 [s, 3 H], 1.27 [s, 3 H], 1.11 [d, J = 7.1 Hz, 3 H], 0.88 [d, J = 6.7 Hz, 3 H], 0.79 [d, J = 6.8 Hz, 3 H]; IR (neat) 2980, 2940, 2880, 2830, 2720, 1730, 1460, 1455, 1380, 1320, 1185, 1150. 1105, 1070, 1015, 995, 970, 880 cm^{-1}.

A solution of the crude aldehyde **53** in 5 mL of anhydrous toluene under Ar was cooled to −78 °C. This solution was added dropwise via cannula to a −78 °C solution of (*S*,*S*)-**1** (4.15 mL, 3.78 mmol, 0.91 M solution in toluene) in 10 mL of anhydrous toluene in the presence of ~300 mg of 4-Å molecular sieves. The reaction mixture was warmed to ~−60 to −50 °C and stirred for 2.5 h at this temperature. After allowing the mixture to gradually warm to room temperature, it was treated with 10 mL of 1 N NaOH and stirred vigorously overnight. The layers were then separated, and the aqueous layer was diluted with 30 mL of brine folowed by extraction with Et_2O (3 × 30 mL). The organic extracts were combined. dried (Na_2SO_4), and concentrated under reduced pressure to provide a yellow oil. Chromatography (flash SiO_2, hexane–Et_2O 7:3) yielded 610 mg (87%) of the desired alcohol **44** as a pale yellow oil. HPLC analysis (15% EtOAc–hexane, flow rate of 0.6 mL/min, retention times: **44**, 15.1; **54**, 16.1 min, refractive index detection) of the crude reaction mixture revealed that ~5% of isomer **54** [the C(25) hydroxyl epimer of **44**] was also produced. This material presumably results from the reaction of aldehyde **53** and the (*Z*)-crotylboronate present as a ca. 4-5% impurity in the batch of (*S*,*S*)-**1** that was used in this experiment. An authentic sample of **54** was prepared by the reaction of **53** and (*S*,*S*)-**2**.

Data for **44**: $[\alpha]^{20}_D$ +15.8 (c 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.86 [ddd, J = 17.2, 10.4, 8.5 Hz, 1 H], 5.10–5.02 [m, 2 H], 4.40 [d, J = 2.3 Hz, 1 H], 3.75–3.67 [m, 2 H], 3.42 [s, 3 H], 3.41 [s, 3 H], 3.33 [dd, J = 7.5, 3.1 Hz, 1 H], 3.21 [bs, 1 H], 2.24 [m, 1 H], 1.87–1.80 [m, 2 H], 1.68 [m, 1 H], 1.29 [s, 6 H, overlapping acetonide methyls], 1.00 [d, J = 7.1 Hz, 3 H], 0.91 [d, J = 6.9 Hz, 3 H], 0.84 [d, J = 6.4 Hz, 3 H], 0.82 [d, J = 6.7 Hz, 3 H]; IR (neat) 3520 (br), 2980, 2930, 1460, 1380, 1225, 1185, 1150, 1070, 995 cm^{-1}. Anal. Calcd for $C_{19}H_{36}O_5$: C, 66.24; H, 10.53. Found: C, 66.07; H, 10.64.

Data for the minor diastereomer **54** [the C(25) epimer of **44**]: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.92 [ddd, J = 18.2, 10.2, 6.6 Hz, 1 H], 5.09–5.01 [m, 2 H], 4.41 [d, J = 1.8 Hz. 1 H], 3.74 [dd, J = 10.8, 3.6 Hz, 1 H], 3.68 [br s, 1 H]. 3.50–3.42 [m, 2 H, partially obscured by methoxyls], 3.44 [s, 3 H], 3.42 [s, 3 H], 2.38 [m, 1 H], 1.85–1.77 [m, 3 H], 1.36 [s, 3 H], 1.30 [s, 3 H], 0.98 [d, J = 6.7 Hz, 3 H], 0.90 [d, J = 6.7 Hz. 3 H], 0.86 [d, J = 7.0 Hz, 3 H], 0.80 [d, J = 7.0 Hz, 3 H]; IR (neat) 3440 (br), 2980, 2930, 2870, 1490, 1455, 1385, 1340, 1180, 1150, 1110, 1070, 1040, 1020, 1000, 840, 820 cm^{-1}; high-resolution mass spectrum (EI) for $C_{18}H_{33}O_5$ ($M^+ - CH_3$), calcd 329.2328; found 329.2332.

(2*R*.3*R*.4*S*.5*S*.6*S*.7*R*.8*R*.9*S*)-7-Acetoxy-3.5-*O*-isopropylidene-1.1-dimethoxy-2.4.6.8-tetramethyldodec-11-ene-3.5.9-triol (46). To a solution of alcohol **44** (402 mg, 1.17 mmol) in 6 mL of anhydrous pyridine under Ar at room temperature was added Ac_2O (0.55 mL, 5.84 mmol) and DMAP (3 mg). The resulting solution was stirred for 12 h at room temperature. The pyridine and excess Ac_2O were removed by coevaporation with n-heptane (3 × 5 mL). The crude product was then chromatographed (flash SiO_2, hexane–Et_2O, 3:1) to yield 444 mg (98%) of the corresponding acetate (**55**) as a colorless oil that crystallized on standing: mp 56–59 °C; $[\alpha]^{20}_D$ +38.8° (c 0.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.66 [ddd, J = 17.1, 13.6, 8.8 Hz, 1 H], 5.10 [dd, J = 9.0, 2.5 Hz, 1 H], 5.00–4.89 [m, 2 H], 4.32 [d, J = 2.2 Hz, 1 H], 3.70 [dd, J = 10.9, 3.7 Hz. 1 H]. 3.44 [s, 3 H], 3.42 [s, 3 H], 3.00 [dd, J = 8.3, 6.6 Hz, 1 H], 2.36 [m, 1 H], 1.95 [s, 3 H], 1.85–1.70 [m, 3 H], 1.26 [s, 3 H], 1.21 [s, 3 H], 0.95 [d, J = 6.9 Hz, 3 H], 0.91 [d, J = 7.1 Hz, 3 H], 0.85 [d, J = 6.7 Hz, 3 H], 0.80 [d, J = 6.8 Hz, 3 H]; IR (neat) 3070, 2980, 2940, 2880, 2850, 1740, 1640, 1460, 1380, 1370, 1240, 1185, 1150, 1105, 1070, 1020, 1000, 970, 950, 905, 880 cm^{-1}. Anal. Calcd for $C_{21}H_{38}O_6$: C, 65.25; H, 9.91. Found: C, 65.26; H, 10.01.

A −78 °C solution of the above acetate **55** (510 mg, 1.32 mmol) in 5 mL of anhydrous MeOH was subjected to the standard ozonolysis procedure described for **18**. The reaction was quenched by the addition of Me_2S (0.5 mL) and then was concentrated under reduced pressure to provide crude aldehyde **45** as a pale yellow oil that was used immediately in the next reaction without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 [d, J = 4.0 Hz, 1 H], 5.44 [dd, J = 9.4, 2.4 Hz, 1 H], 4.41 [d. J = 2.4 Hz, 1 H], 3.71 [dd, J = 10.9, 3.7 Hz, 1 H], 3.44 [s, 3 H], 3.42 [s, 3 H], 3.03 [dd, J = 8.7, 6.4 Hz, 1 H], 2.58 [m, 1 H], 1.99 [s, 3 H], 1.84–1.63 [m, 3 H], 1.26 [s, 3 H], 1.23 [s, 3 H], 1.06 [d, J = 7.1 Hz, 3 H], 0.93 [d, J = 6.9 Hz, 3 H], 0.87 [d, J = 6.6 Hz, 3 H], 0.80 [d, J = 6.9 Hz, 3 H]; IR (neat) 2980, 2940, 2880, 2830, 2720, 1730, 1460, 1380, 1235, 1185, 1150, 1110, 1070, 1020, 1000 cm^{-1}.

The above crude aldehyde was dissolved in 1 mL of anhydrous toluene and cooled to −78 °C. This solution was then added dropwise via cannula to a −78 °C solution of (*R*,*R*)-**16** (3.51 mL, 2.64 mmol, 0.75 M solution in toluene) and ~200 mg of 4-Å molecular sieves in 5 mL of toluene under Ar. The resulting mixture was maintained at −78 °C for 4 h and then allowed to gradually warm to room temperature. The solvent was then removed under reduced pressure to provide a crude residue that was chromatographed (hexane–Et_2O, 7:3, flash SiO_2) to give 377 mg (70% overall) of the desired homoallyl alcohol **46** (which crystallized on standing) along with 30 mg of the minor diastereomer **56** [the C(27) epimer of **46**]. HPLC analysis (30% EtOAc–hexane. flow rate of 0.9 mL/min, retention time: **46**, 9.9; **56**, 13.0 min, refractive index) of the crude reaction mixture showed that the two homoallylic alcohols **46** and **56** were produced in a ratio of 91:9.

Data for **46**: mp 104–107 °C; $[\alpha]^{20}_D$ +15.2° (c 1.56, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.81 [m, 1 H]. 5.17 [dd, J = 10.7, 2.0 Hz, 1 H], 5.10–5.00 [m, 2 H], 4.41 [d, J = 2.3 Hz, 1 H], 3.70 [dd, J =10.9, 3.7 Hz. 1 H], 3.47 [m, 1 H, partially masked by OMe], 3.44 [s, 3 H],

3.42 [s, 3 H], 3.08 [d, J = 3.6 Hz, 1 H], 2.99 [dd, J = 8.8, 6.2 Hz, 1 H], 2.37 [m, 1 H], 2.08 [m, 1 H, masked by acetate methyl], 2.07 [s, 3 H], 1.85–1.79 [m, 2 H], 1.69–1.63 [m, 2 H], 1.26 [s, 3 H], 1.19 [s, 3 H], 0.89 [d, J = 7.0 Hz, 3 H], 0.88 [d, J = 6.7 Hz, 3 H], 0.83 [d, J = 7.3 Hz, 3 H], 0.80 [d, J = 7.3 Hz, 3 H]; IR ($CDCl_3$) 3510, 2980, 2904, 2910, 2830, 1715, 1640, 1455, 1380, 1325, 1310, 1255, 1240, 1225, 1175, 1150, 1110, 1065, 1020, 1000, 970, 915 cm^{-1}. Anal. Calcd for $C_{23}H_{42}O_7$: C, 64.15; H, 9.83. Found: C, 64.04; H, 9.91.

Data for minor diastereomer **56**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.83 [m, 1 H], 5.26 [dd, J = 6.8, 1.4 Hz, 1 H], 5.13–5.06 [m, 2 H], 4.41 [d, J = 2.1 Hz, 1 H], 3.71 [dd, J = 11.0, 3.8 Hz, 1 H], 3.50–3.40 [m, 1 H, partially masked by methoxyls], 3.44 [s, 3 H], 3.42 [s, 3 H], 3.16 [dd, J = 9.1, 6.8 Hz, 1 H], 2.67 [d, J = 3.8, 1 H], 2.40 [m, 1 H], 2.12–2.02 [m, 1 H, partially masked by acetate methyl], 2.03 [s, 3 H], 1.96–1.65 [m, 4 H], 1.30 [s, 3 H], 1.28 [s, 3 H], 0.94–0.85 [m, 9 H, overlapping methyl groups], 0.80 [d, J = 6.9 Hz, 3 H]; IR ($CDCl_3$) 3450 (br), 3070, 2980, 2930, 1725, 1640, 1460, 1380, 1370, 1250, 1225, 1175, 1145, 1105, 1065, 1020, 995, 970, 955 cm^{-1}; high-resolution mass spectrum (EI) for $C_{23}H_{41}O_6$ (M^+ – OH), calcd 413.2903; found, 413.2902.

(2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*R*,9*S*)-7-Acetoxy-3,5-isopropylidene-2,4,6,8-tetramethyl-1,1,7-trimethoxydodec-11-ene-3,5-diol (40). To a –20 °C solution of alcohol **46** (100 mg, 0.25 mmol) in 1 mL of anhydrous THF was added iodomethane (1.50 mL, 24.8 mmol). This solution was then treated dropwise with a slurry of KO^{t}Bu in THF (1.24 mL, 1.24 mmol, 1.0 M solution). KI precipitated upon addition of the base. The resulting mixture was stirred for 1 h at –20 °C and then was partitioned between 5 mL of Et_2O and 5 mL of saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a pale yellow oil. Purification of the crude product by chromatography (hexane–Et_2O 7:3, flash SiO_2) yielded 78 mg (70%) of the desired methyl ether **40** along with 11 mg of an isomeric methyl ether (**57**) resulting from acyl migration prior to methylation.

Data for **40**: mp 49–51 °C; $[\alpha]^{20}_D$ +3.7° (c 0.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.71 [m, 1 H], 5.34 [dd, J = 9.3, 1.3 Hz, 1 H], 5.10–5.00 [m, 2 H], 4.42 [d, J = 2.3 Hz, 1 H], 3.69 [dd, J = 11.0, 3.9 Hz, 1 H], 3.44 [s, 3 H], 3.42 [s, 3 H], 3.29 [s, 3 H], 3.07 [dt, J = 7.0, 1.7 Hz, 1 H], 2.99 [dd, J = 7.1, 7.1 Hz, 1 H], 2.46 [m, 1 H], 2.11 [m, 1 H], 2.01 [s, 3 H], 1.84–1.69 [m, 4 H], 1.26 [s, 3 H], 1.23 [s, 3 H], 0.89 [d, J = 7.1 Hz, 3 H], 0.85–0.71 [m, 9 H, overlapping methyls]; IR ($CHCl_3$) 3080, 2980, 2920, 1740, 1460, 1380, 1240, 1190, 1150, 1070, 1020, 1000, 970, 950 cm^{-1}. Anal. Calcd for $C_{24}H_{44}O_7$: C, 64.83; H, 9.98. Found: C, 65.10; H, 9.73.

Data for minor regioisomer **57**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 [m, 1 H], 5.19 [dt, J = 13.5, 1.7 Hz, 1 H], 5.08–4.99 [m, 2 H], 4.44 [d, J = 2.0 Hz, 1 H], 3.70 [dd, J = 10.4, 2.7 Hz, 1 H], 3.46 [s, 3 H], 3.42 [s, 3 H], 3.37 [s, 3 H], 3.31 [dd, masked by OMe, 1 H], 3.20 [dd, J = 9.0, 5.2 Hz, 1 H], 2.41 [m, 1 H], 2.28 [m, 1 H], 2.02 [s, 3 H], 1.97–1.56 [m, 4 H], 1.31 [s, 3 H], 1.28 [s, 3 H], 0.90 [d, J = 6.1 Hz, 3 H], 0.83–0.78 [m, 9 H, overlapping methyls]; IR ($CDCl_3$) 2970, 2920, 2820, 1720, 1635, 1450, 1370, 1240, 1220, 1180, 1140, 1100, 1060, 1010, 980, 955 cm^{-1}, high-resolution mass spectrum (EI) for $C_{21}H_{38}O_6$ (M^+ – C_3H_6O (acetone)), calcd 386.2668; found 386.2690.

(2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*R*,9*S*)-7-Acetoxy-3,5-dihydroxy-3,5-*O*-isopropylidene-9-methoxy-2,4,6,8-tetramethyldodec-11-enal (35). The Rifamycin S C(19)–C(29) Segment. A solution of dimethyl acetal **40** (5.0 mg, 0.012 mmol) in 1 mL of reagent grade acetone (0.2% H_2O) containing 0.5 mg of p-TsOH was stirred for 4 h at room temperature. The reaction was then quenched by the addition of 10 mg of solid $NaHCO_3$. After stirring for 10 min, the reaction mixture was filtered through a cotton plug. The filtrate was concentrated under reduced pressure to provide 4.3 mg (96%) of aldehyde **35** as a colorless oil: $[\alpha]^{20}_D$ –5.8° (c 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.62 [d, J = 3.3 Hz, 1 H], 5.73 [m, 1 H], 5.34 [dd, J = 9.8, 1.0 Hz, 1 H], 5.10–5.01 [m, 2 H], 3.95 [dd, J = 10.8, 4.1 Hz, 1 H], 3.28 [s, 3 H], 3.12–3.05 [m, 2 H], 2.52–2.32 [m, 2 H], 2.17–2.11 [m, 1 H], 2.08–1.90 [m, 1 H], 2.00 [s, 3 H], 1.82–1.72 [m, 2 H], 1.24 [s, 3 H], 1.23 [s, 3 H], 0.98 [d, J = 7.1 Hz, 3 H], 0.91 [d, J = 7.2 Hz, 3 H], 0.85 [d, J = 6.8 Hz, 3 H], 0.82 [d, J = 7.0 Hz, 3 H]; IR (neat) 3080, 2980, 2940, 2920, 2880, 2865, 2710, 1740, 1640, 1465, 1455, 1380, 1250, 1195, 1180, 1150, 1110, 1085, 1050, 1025, 1005, 970, 930, 890, 880 cm^{-1}; high-resolution mass spectrum (EI) for $C_{21}H_{35}O_6$ (M^+ – CH_3), calcd 383.2434; found, 383.2459.

Correlation of 35 with the Rifamycin Degradation Product 47. To a solution of **35** (18 mg, .046 mmol) in 3 mL of anhydrous EtOH at –50 °C under Ar was added $NaBH_4$ (10 mg, 0.26 mmol). The reaction was allowed to gradually warm to room temperature. After 30 min, the reaction was quenched with ~1 mL of H_2O, and the resulting mixture was extracted with Et_2O (3 × 3 mL). Drying (Na_2SO_4) followed by concentration under reduced pressure gave 14 mg (81%) of the primary alcohol **58** as a white solid.

Crude **58** (14 mg, 0.037 mmol) was dissolved in 1 mL of anhydrous CH_2Cl_2 under Ar at room temperature. To this solution was added i-Pr_2NEt (0.032 mL, 0.185 mmol) followed by SEM–Cl (0.020 mL, 0.112 mmol). The resulting mixture was stirred for 1 h and then quenched by pouring into 5 mL of saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were concentrated in vacuo giving a pale yellow oil that was purified by passing through a short plug of flash SiO_2 (hexane–Et_2O 1:1). Concentration of the filtrate yielded 22 mg of SEM ether **59** that was contaminated with residual SEM–Cl.

A major fraction of the material generated in the last reaction (~16 mg) was subjected to the standard ozonolysis procedure with the exception that the reaction was worked up by the addition of ~100 mg of $NaBH_4$ (large excess) to the –78 °C solution of α-methoxyhydroperoxide. Upon warming to room temperature, the reaction was quenched by the dropwise addition of 1 mL of H_2O. The aqueous was then extracted with Et_2O (3 × 2 mL). Drying (Na_2SO_4) followed by concentration under reduced pressure provided the crude primary alcohol **60** as a colorless oil.

Crude **60** (~10 mg) was evaporated twice from anhydrous THF (1 mL) and then dissolved in 2 mL of anhydrous THF under Ar. $LiAlH_4$ (~50 mg) was then added and the reaction mixture warmed to 40 °C. After 20 min, the reaction was cooled to 0 °C and quenched by the slow addition of wet Et_2O. The mixture was then diluted with NH_4Cl and extracted with Et_2O (4 × 5 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide a colorless oil that was purified by preparative TLC (0.25-mm silica gel plate, Et_2O). In this manner, 7 mg of **47** was obtained as a colorless oil. This material proved identical in all respects with a sample of naturally derived **47** kindly provided by Professor Masamune.

Data for **47**: $[\alpha]^{20}_D$ +3.9 (c 0.5, $CHCl_3$), synthetic; $[\alpha]^{20}_D$ +4.2° (c 1.1, $CHCl_3$), natural; ^1H NMR (250 MHz, $CDCl_3$) δ 4.68 [A of AB, J = 6.6 Hz, 1 H], 4.65 [B of AB, J = 6.6 Hz, 1 H], 3.96 [br d, J = 10.6 Hz, 1 H], 3.82–3.75 [m, 3 H], 3.60–3.55 [m, 6 H], 3.47 [s, 3 H], 3.41 [dd, J = 9.6, 6.5 Hz, 1 H], 3.35 [dd, J = 7.3, 3.7 Hz, 1 H], 2.00–1.55 [m, 6 H], 1.32 [s, 3 H], 1.30 [s, 3 H], 0.97 [d, J = 6.6 Hz, 3 H], 0.94 [d, J = 6.4 Hz, 3 H], 0.92–0.85 [m, 5 H], 0.77 [d, J = 7.0 Hz, 3 H], 0.02 [s, 9 H]; ^{13}C NMR (100 MHz, $CDCl_3$) (naturally derived **47**) δ 95.3, 80.8, 79.9, 77.2, 71.6, 70.4, 70.1, 64.9, 61.2, 58.7, 38.8, 37.0, 35.3, 34.4, 33.6, 25.0, 23.3, 18.1, 13.4, 12.1, 10.7, 10.2, –1.4; (synthetic **47**) δ 95.3, 80.8, 79.9, 77.2, 71.7, 70.5, 70.1, 64.9, 61.2, 58.7, 38.8, 36.9, 35.3, 34.3, 33.6, 25.0, 23.4, 18.1, 13.4, 12.1, 10.7, 10.2, –1.4; IR ($CDCl_3$) 3480 (br), 2960, 2930, 2880, 1455, 1380, 1250, 1225, 1185, 1145, 1105, 1030, 1005, 860, 840 cm^{-1}. Anal. Calcd for $C_{25}H_{52}O_7Si$: C, 60.94; H, 10.64. Found: C, 61.00; H, 10.84.

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