Experimental Section

General Methods. General experimental procedures were as previously described.[18] Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Sodium borodeuteride was obtained from MSD Isotopes and was stated to have an isotopic purity of 98 at. % ^2H. ^1H NMR spectra were obtained in D_2O by using dioxane as internal standard.

Sodium (2*R*)-[2-$^2H_1$]Propanoate. Ethyl (2*S*)-2-(*p*-(tolylsulfonyl)oxy)propionate was prepared from (*S*)-(−)-ethyl lactate (Aldrich Chemical Co.) as previously described.[13] This ester 40.4 g, 0.158 mmol) was stirred by magnetic stirrer with sodium borodeuteride (3.3 g, 0.079 mmol) at 100 °C for 48 h under 2–3 mmHg of pressure. The volatile products were collected in a −78 °C trap and identified by GC as ethyl propionate and triethyl borate. This mixture was hydrolyzed with sodium hydroxide (0.6 M in 50% aqueous ethanol) at room temperature for 2 h, and the solution then extracted with ether to remove organic material. The aqueous layer was then acidified with dilute HCl and extracted with ether (3 × 200 mL), and the ether washed (water, brine) and dried. Careful evaporation of the ether gave free propionic acid, which was neutralized to pH 8 with 0.6 M NaOH, and the solution evaporated to give sodium (2*R*)-[2-$^2H_1$]propionate: yield 1.3 g (9.0%); $[\alpha]^{28}_D$ = −0.87° (*c* 6.9, H_2O) [lit.[13] $[\alpha]^{28}_D$ −0.88° (*c* 10, H_2O); ^1H NMR δ 1.01 (dt, 3 H, *J* = 7.7, 0.9 Hz), 2.12 (qt, 1 H, *J* = 7.7, 2.3 Hz).

Sodium (2*S*)-[2-$^2H_1$]Propanoate. (*R*)-(+)-Methyl lactate (Aldrich Chemical Co.) was converted to methyl (2*R*)-2-(*p*-(tolylsulfonyl)oxy)propionate, and this ester (43.1 g) was reduced to sodium (2*S*)-[2-$^2H_1$]propanoate by the method described above: yield 1.90 g (11.7%); $[\alpha]^{28}_D$ + 0.81 (*c* 2, H_2O); ^1H NMR identical with that of the 2*R* isomer.

Culture Conditions. *Streptomyces griseo-olivaceus*, strain C23201-NS7 obtained from Lederle Laboratories, was maintained on agar slants at 4 °C until needed. The mycelium from one slant was transferred to an inoculum medium of 50 mL in each of two baffled 240-mL flasks; the inoculum medium consisted of yeast extract (0.5%), beef extract (0.3%), tryptose (0.5%), dextrin (2.4%), dextrose (0.5%), and $CaCl_2$ (0.4%) in distilled water. Incubation was carried out at 28 °C and on a rotary shaker at 200 rpm for 4 days. A second stage inoculum was then prepared by transferring 5% of the first stage inoculum into each of four flasks containing 50 mL of the same medium and incubating for 3 days at 28 °C and 200 rpm. The second stage inoculum (4 × 10 mL) was then transferred into four 1000-mL baffled flasks containing the fermentation medium: dextrose (1.5%), glycerol (1.5%), soybean flour (1.5%), $CaCO_3$ (0.1%), and NaCl (0.3%). Incubation was carried out for 6 days at 28 °C and 200 rpm, with addition of labeled sodium propionate after 28 h.

Isolation of Ravidomycin. Ethyl acetate (300 mL) was added to each fermentation flask, and the contents were stirred overnight and then filtered through Hyflo SuperCel. The layers were separated, and the aqueous layer was reextracted with EtOAc; the organic extracts were then combined, washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (acetone:hexanes 60:40) to yield ravidomycin (100–148 mg) as a yellow powder, homogeneous on TLC (silica gel, acetone:hexanes 60:40) with the same R_f (0.23) as an authentic sample.[12]

Analysis of Deuterium Incorporation. Ravidomycin (50 mg) was dissolved in 5% KOH (1.76 mL) and treated with 3% H_2O_2 (0.44 mL). The solution was stirred at 80 °C for 4 h with addition of three additional portions of H_2O_2 at 1-h intervals. The resulting solution was cooled, acidified with dilute HCl, and extracted with EtOAc (3 × 15 mL). The organic extracts were combined, washed, dried (Na_2SO_4), and evaporated to yield a crude yellow solid. This material was dissolved in 95% EtOH and treated with an ethereal solution of diazomethane until the yellow color persisted. Excess diazomethane was destroyed (AcOH), and the solution was evaporated. The crude product (10 mg) was analyzed by GC MS (HP5 column, 25m × 0.32 mm, 75–200 °C, VG7070E-HF instrument) to yield four major peaks with retention times of 6.85, 7.97, 9.12, and 11.78 min and relative areas of 0.35, 0.30, 0.20, and 0.15. The peak at 7.97 min (estimated yield of 6%) had a mass spectrum consistent with compound **2**: *m/z* 250 (M^+, 13), 219 (100), 187 (15), 160 (10), 145 (7), 118 (3), 102 (8), 77 (7). MS data for the labeled compounds are given in Table I.

Acknowledgment. We thank Dr. Don B. Borders of Lederle Laboratories for gifts of ravidomycin and *S. griseo-olivaceus* strain C23201-NS7.

Registry No. 1, 74622-75-6; 2, 123701-27-9; CH_3CH_2COONa, 137-40-6; CH_3CD_2COONa, 21386-58-3; (*R*)-$CH_3CHDCOONa$, 73493-56-8; (*S*)-$CH_3CHDCOONa$, 123701-28-0; (*S*)-(−)-ethyl lactate, 687-47-8; (*R*)-(+)-methyl lactate, 17392-83-5; ethyl (2*S*)-2-((*p*-tolylsulfonyl)oxy)propionate, 57057-80-4; methyl (2*S*)-2-((*p*-tolylsulfonyl)oxy)propionate, 109579-04-6.

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Stereochemical Aspects of the Additions of Anti-Selective, Crotyl Organometallic Reagents to α-Alkoxy Aldehydes

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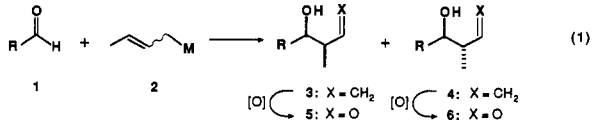
Introduction

The addition of crotyl organometallic reagents **2** to aldehydes **1** according to eq 1 constitutes a useful reaction



(1)

that has been widely exploited in synthetic organic chemistry.[2] This process results in the formation of two contiguous stereogenic centers, and either the syn- or the anti-adducts **3** and **4**, respectively, may be preferentially produced.[2-9] The importance of this reaction lies in the

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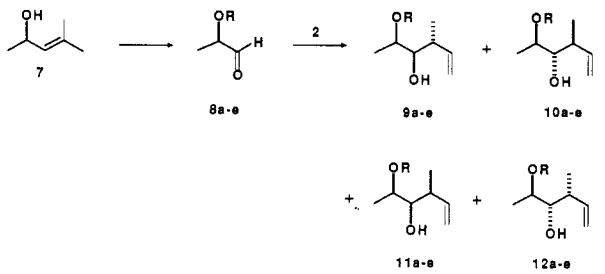
Table I. Diastereomer Ratios[a] from Additions of Crotyl Organometallics to α-Alkoxy Aldehydes 8a–e

R	M					
	MgCl	Cp_2TiCl	Cp_2ZrCl	$Ti(OPh)_3$	Cr(II)Cl	$CrCl_2(THF)_3$
Bn	31:27:19:23 (94%)	38:43:7:12[b] 33:29:27:11[c] (80–85%)	42:38:14:6[b] 38:24:26:12[c] (80–85%)	50:50:0:0 (83%)	29:71:0:0 (80%)	50:37:8:5 (60%)
$BnOCH_2$	24:28:22:26 (89%)	38:45:7:10 (52%)	35:30:20:15 (66%)	43:41:8:8 (58%)		
t-$BuMe_2Si$	32:24:16:28 (66%)	35:29:18:36 (67%)	38:29:14:19 (77%)	46:48:4:2 (55%)		28:20:15:37 (90%)
MEM		39:45:7:9 (68%)	38:29:31:2 (73%)			
Ph_3C					25:75:0:0 (94%)	

[a] Ratio (percent normalized to 100) of adducts **9a–e**:**10a–e**:**11a–e**:**12a–e**. [b] At 0 °C. [c] At −78 °C.

Scheme I



Series a: R = Bn
b: R = CH_2OBn
c: R = TBDMS
d: R = MEM
e: R = CPh_3

fact that the adducts **3** and **4** may be converted into the corresponding aldehydes **5** and **6** by oxidative scission of the carbon–carbon double bond. The overall transformation is thereby rendered the synthetic equivalent of the aldol reaction with the potential advantage that the carbonyl function resides in latent form until its unmasking at the appropriate moment.

During the course of a recent synthetic investigation, we had occasion to examine the diastereoselectivity in the additions of various crotyl organometallic reagents to α-alkoxy aldehydes according to Scheme I. In the reactions of crotyl organometallic reagents with α-substituted aldehydes, not only is there the question of simple diastereoselection (i.e., syn/anti) but there is also a second issue that arises involving the diastereofacial selectivity of the process. Typically, the additions of crotyl organometallic reagents to α-substituted aldehydes proceeds with modest levels of diastereoselectivity in a stereochemical sense that may be qualitatively predicted on the basis of Cram's rule for asymmetric induction[10] or one of its more recent variants.[11] However, in the case of α-alkoxy (and β-alkoxy) carbonyl compounds, internal chelation often provides a powerful stereochemical control element to direct additions to the carbonyl function from the less hindered face of the intermediate cyclic dioxametallocycle.[12] However, there have been few investigations of the diastereoselectivity of additions of crotyl organometallics to such aldehydes.[4d,e,5d,e] Thus, we undertook an examination of the reactions of several anti-selective crotyl organometallic reagents with α-alkoxy aldehydes bearing different protecting groups on the oxygen to evaluate the relative importance of chelation control in these processes.[13]

Results

To focus the investigation upon the effect of having an alkoxy group appended to the α-carbon atom of the aldehyde, it was deemed necessary to minimize steric considerations by employing substrates in which the two substituents on the carbon adjacent to the carbonyl function were approximately the same size. To this end, the five representative α-alkoxy aldehydes **8a–e** were prepared from the known alcohol **7**[14] according to established procedures[15] that proceeded by initial O-protection followed by ozonation with excess ozone. Reactions of **8a–e** with a variety of crotyl organometallic reagents **2** in tetrahydrofuran (THF)[16] provided variable mixtures of 1,2-adducts **9a–e**, **10a–e**, **11a–e**, and **12a–e** as summarized in Table I. Product ratios from the reactions of **8a–e** with crotyl organometallic reagents were initially obtained on the crude reaction mixtures by analytical HPLC (μ-Porasil). After conversion of these mixtures into the mixture of saturated diols **13–16** by O-deprotection and catalytic hydrogenation (vide infra), composition and structural assignments were made by both analytical HPLC and ^{13}C NMR comparisons with authentic samples.

As might be anticipated, it was not possible to determine directly from ^1H and ^{13}C NMR spectra the relative ster-

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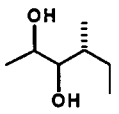
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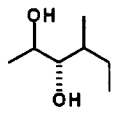
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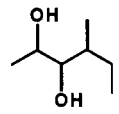
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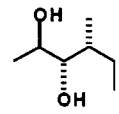
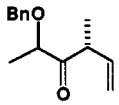

16

eochemistry of the four diastereomers. Fortunately, the 3,5-dinitrobenzoates of **9a** and **11a** were crystalline, and consequently single-crystal X-ray analyses revealed their relative stereochemistries.[17] Since crystalline derivatives of **10a** and **12a** could not be obtained, the structures of these alcohols were established by chemical correlation with their respective epimers **11a** and **9a**. Thus, oxidation of the homoallylic alcohols **9a** and **12a** with pyridinium dichromate[18] gave the same ketone **17**; similarly, oxidation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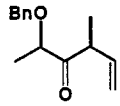
18

of **10a** and **11a** provided the same ketone **18**. Having thus unequivocally determined the relative stereochemistry of **9a–12a**, it remained to make the necessary correlations with the adducts obtained upon addition of the crotyl organometallic reagents to the remaining aldehydes **8b–e**. In the event, **9a–12a** were each transformed into the corresponding saturated diols **13–16** by catalytic hydrogenation (40 psi, 10% Pd/C). The mixtures of adducts **9b–e—12b–e** were also converted to the saturated diols **13–16** by sequential removal of the hydroxyl protecting group and catalytic hydrogenation of the olefin.

Discussion

Not unexpectedly,[3] the addition of crotyl magnesium chloride (**2**, M = MgCl) to aldehydes **8a–c** proceeded with a relatively low level of both simple (anti/syn) diastereoselectivity and diastereofacial selectivity.[19] However, additions of the crotyl chromium[5] (**2**, M = CrCl, $CrCl_2$), titanium[6] (**2**, M = Cp_2TiCl, $(PhO)_3Ti$), and zirconium[7] (**2**, M = Cp_2ZrCl) reagents to aldehydes lacking an α- or β-alkoxy group are known to proceed with a high level of anti selectivity, and this trend was observed in the present study; the formation of the anti-isomers **9a–e** and **10a–e** dominated over the corresponding syn-adducts **11a–e** and **12a–e**. When the α-carbon of the aldehydic partner is a stereogenic center bearing only alkyl substituents, additions of these crotyl organometallics typically proceed preferentially to give the Cram[10,11] product with at best modest (e.g., 1–3:1)[5b,c,7a] diastereoselectivity. Somewhat surprisingly, the presence of the α-alkoxy substituent on the aldehydes **8a–e** had virtually no effect upon the diastereofacial selectivity of the reactions; ratios of "chelation-controlled" products **9a–e** and **11a–e** to the "non-chelation-controlled" products **10a–e** and **12a–e** varied disappointingly from 0.8 to 1.8:1. In this context it might be noted that there are several examples in which crotylchromium reagents added with high levels of diastereofacial selectivity to β-alkoxy aldehydes, but the effect was ruled to be a consequence of steric factors, not chelation.[5d,e] Interestingly, we did observe that there was a slight increase in the formation of the "chelation-controlled" products **9a** and **11a** in the additions of $Cp_2Ti(CH_2CH{=}CHCH_3)Cl$ and $Cp_2Zr(CH_2CH{=}CHCH_3)Cl$ to **8a** when the reactions were executed at −78 °C rather than the usual temperature of 0 °C; however, this enhancement in diastereofacial selectivity was attended with an erosion in the anti/syn selectivity from 4.2:1 at 0 °C to 1.6:1 at −78 °C. The reasons for this phenomenon cannot be presently explained.

Conclusions

Although we had hoped that the anti-selective additions of crotyl titanium, zirconium, and chromium reagents to α-alkoxy aldehydes **8a–e** might ensue with a significant level of chelation control, this was not observed experimentally. These results may be contrasted with the magnesium bromide catalyzed addition of tri-*n*-butylcrotylstannane to **8a** and **8d**, which proceeded with essentially complete diastereofacial selectivity and with high syn/anti selectivity (ca. 10:1), in close analogy with previous work of Keck.[4d] A higher degree of diastereoselectivity in additions to α-alkoxy aldehydes might be obtained through the agency of chiral crotyl boronates, which have been examined extensively by others,[9d,g-i] as nucleophilic partners.

Experimental Section

General Procedures. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) was dried by distillation under nitrogen from sodium or potassium/benzophenone ketyl immediately prior to use. Reactions involving air- and/or moisture-sensitive reagents were conducted under an atmosphere of argon, and the glassware was flame dried under a stream of dry argon prior to use. The purity of all title compounds was judged to be ≥95% by GC and/or ^1H and ^{13}C NMR spectral determinations. Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentaplet; m, multiplet; comp, complex; and br, broad. Analytical HPLC analyses were determined using a μ-Porasil column; preparative high-performance liquid chromatography (HPLC) was performed using Porasil A columns.

The ratio of the four separable diastereomeric adducts **9b–e**, **10b–e**, **11b–e**, and **12b–e** from each reaction was initially determined by analytical HPLC. The resulting mixture was then converted into a mixture of the saturated, diastereoisomeric diols **13–16** by removal of the hydroxyl protecting group and catalytic hydrogenation. The ^{13}C NMR spectrum of the resulting mixture was then obtained and correlated with spectra of the pure diols **13–16**, which had been prepared from the separated adducts **9a–12a**, for initial structural assignments; the product ratios of stereoisomers determined by ^{13}C NMR by multiple peak integrations of these mixtures of diols **13–16** were consistent with the stereoisomeric ratios previously obtained by HPLC analyses of the mixtures of adducts **9b–e—12b–e**.

Addition of Crotylmagnesium Chloride to 8a. To crotylmagnesium chloride (0.75 M, 1.5 mL, 1.10 mmol) in THF was added slowly 2-(benzyloxy)propanal **8a** (160 mg, 1.0 mmol) at −78 °C under argon with stirring. The reaction mixture was raised to room temperature gradually (1 h) and then poured into a mixture of water (8 mL) and ether (25 mL). The aqueous layer was extracted with ether (3 × 20 mL). The extracts were combined, washed with water (3 × 8 mL) and brine (2 × 8 mL), and dried ($MgSO_4$). The excess solvents were evaporated under reduced pressure to give a crude mixture (207 mg, 94% yield) of **9a**, **10a**, **11a**, and **12a**, which was readily separated by HPLC (15:1

(17) The single-crystal X-ray analyses of the 3,5-dinitrobenzoates derived from **9a** and **11a** were determined by Dr. Steven B. Larson (Department of Chemistry, The University of Texas), who we thank; these results will be reported independently.

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hexane/ethyl acetate) to give pure samples of the four known[9i] olefinic diols **9a** (59 mg, 31%), **10a** (27 mg, 27%), **11a** (36 mg, 19%), and **12a** (43 mg, 23%) as thick colorless oils. The 3,5-dinitrobenzoates of **9a** and **11a** were prepared by treatment of **9a** and **11a** with 3,5-dinitrobenzoyl chloride (1.5 equiv), Et_3N (1.5 equiv), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 at room temperature (18 h).

(2*R,3*R**,4*R**)-2-(Benzyloxy)-4-methyl-5-hexen-3-ol (9a):**[9i] ^1H NMR (200 MHz) δ 7.40–7.27 (comp, 5 H), 5.38 (m, 1 H), 5.10–4.99 (comp, 2 H), 4.67 (d, 1 H, J = 11.4 Hz), 4.42 (d, 1 H, J = 11.4 Hz), 3.49 (p, 1 H, J = 6.2 Hz), 3.32 (dd, 1 H, J = 4.4, 6.2 Hz), 2.37 (m, 1 H), 1.22 (d, 3 H, J = 6.2 Hz), 1.08 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (20 MHz) δ 139.8, 138.3, 128.4, 127.8, 127.7, 115.1, 78.2, 76.5, 70.8, 40.3, 17.7, 15.4. The 3,5-dinitrobenzoate derivative of **9a** afforded crystals suitable for single-crystal X-ray analysis (see supplementary material): mp (from hexane) 132.5–134 °C; ^1H NMR (360 MHz) δ 9.12 (t, 1 H, J = 2.0 Hz), 8.97 (d, 2 H, J = 2.0 Hz), 7.19–7.08 (comp. 5 H), 5.72 (m, 1 H), 5.07–4.97 (comp. 2 H), 4.60 (d, 1 H, J = 12.0 Hz), 4.30 (d, 1 H, J = 12.0 Hz), 3.72 (p, 1 H, J = 6.2 Hz), 2.69 (m, 1 H), 1.20 (d, 1 H, J = 6.2 Hz), 0.97 (d, 1 H, J = 6.8 Hz); ^{13}C NMR (90 MHz) δ 162.3, 158.6, 138.6, 138.1, 134.2, 129.4, 128.2, 127.6, 127.5, 122.1, 116.6, 82.1, 74.1, 70.9, 39.1, 17.3, 15.7; IR ($CDCl_3$) 1725, 1550, 1350, 1280, 1175 cm^{-1}; MS, m/e 414.14209 ($C_{21}H_{22}N_2O_7$ requires 414.14270), 397, 354, 195, 165, 91 (base).

(2*R,3*S**,4*S**)-2-(Benzyloxy)-4-methyl-5-hexen-3-ol (10a):**[9i] ^1H NMR (200 MHz) δ 7.40–7.25 (comp, 5 H), 5.86 (m, 1 H), 5.16–5.05 (comp, 2 H), 4.62 (d, 1 H, J = 11.8 Hz), 4.49 (d, 1 H, J = 11.8 Hz), 3.62–3.49 (comp, 2 H), 2.53 (m, 1 H), 1.93 (br, 1 H), 1.22 (d, 3 H, J = 6.1 Hz), 0.98 (d, 3 H, J = 6.5 Hz); ^{13}C NMR (20 MHz) δ 140.5, 138.4, 128.4, 127.6, 115.3, 76.4, 75.7, 70.6, 39.5, 16.3, 13.7.

(2*R,3*R**,4*S**)-2-(Benzyloxy)-4-methyl-5-hexen-3-ol (11a):**[9i] ^1H NMR (200 MHz) δ 7.35–7.25 (comp, 5 H), 5.77 (m, 1 H), 5.05–4.95 (comp, 2 H), 4.64 (d, 1 H, J = 11.4 Hz), 4.41 (d, 1 H, J = 11.4 Hz), 3.62 (m, 1 H), 3.24 (dd, 1 H, J = 4.5, 6.3 Hz), 2.39 (m, 1 H), 2.22 (br, 1 H), 1.23 (d, d, 3 H, J = 6.2 Hz), 1.06 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (20 MHz) δ 141.7, 138.4, 128.4, 127.8, 127.7, 114.5, 78.3, 70.9, 40.8, 16.2, 15.0. The 3,5-dinitrobenzoate derivative of **11a** afforded crystals suitable for single-crystal X-ray analysis (see supplementary material): mp (from hexane) 113–115 °C; ^1H NMR (360 MHz) δ 9.21 (t, 1 H, J = 2.0 Hz), 9.10 (d, 2 H, J = 2.0 Hz), 7.28–7.18 (comp, 5 H), 5.77 (ddd, J = 7.3, 10.2, 17.3 Hz), 5.16 (dd, 1 H, J = 5.0, 6.8 Hz), 5.12–5.04 (comp, 2 H), 4.66 (d, 1 H, J = 11.8 Hz), 4.37 (d, 1 H, J = 11.8 Hz), 3.86 (m, 1 H), 2.87 (m, 1 H), 1.24 (d, 3 H, J = 6.4 Hz), 1.07 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (90 MHz) δ 162.4, 148.8, 139.5, 138.4, 134.3, 129.4, 128.3, 127.5, 122.2, 116.0, 82.1, 74.1, 71.1, 38.4, 16.2, 15.1; IR ($CDCl_3$) 1725, 1550, 1350, 1280 cm^{-1}; MS m/e 414.14209 ($C_{21}H_2O_7$ requires 414.14270), 354, 195, 165, 91 (base).

(2*R,3*S**,4*R**)-2-(Benzyloxy)-4-methyl-5-hexen-3-ol (12a):**[9i] ^1H NMR (200 MHz) δ 7.32–7.16 (comp, 5 H), 5.59 (ddd, 1 H, J = 8.1, 10.2, 17.4 Hz), 5.02–4.89 (comp, 2 H), 4.50 (d, 1 H, J = 11.7 Hz), 4.39 (d, 1 H, J = 11.7 Hz), 3.54–3.45 (comp, 2 H), 2.30–1.96 (comp, 2 H), 1.11 (d, 3 H, J = 6.0 Hz), 1.02 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (20 MHz) δ 140.4, 138.5, 128.4, 127.6, 115.0, 75.9, 75.8, 70.5, 40.2, 16.3, 12.9.

General Procedure for Reduction of Homoallylic Alcohols 9a, 10a, 11a, and 12a. A 5-mL reaction vial containing the allylic alcohol **9a–12a** (25–50 mg), 5% Pd/C (5 mg), and 1 mL of MeOH was shaken under an atmosphere of hydrogen (30 psi) for 10 h. The catalyst was removed by filtration, and the solvents were evaporated under reduced pressure to give the pure diols **13–16** in approximately 90% yields as colorless oils.

(2*R,3*R**,4*R**)-4-Methylhexane-2,3-diol (13):** ^1H NMR (360 MHz) δ 3.84 (m, 1 H), 3.13 (t, 1 H, J = 5.1 Hz), 2.20–2.40 (br s, 1 H), 1.54 (m, 2 H), 1.19 (d, 3 H, J = 6.3 Hz), 1.16 (m, 1 H), 0.94 (d, 3 H, J = 6.8 Hz), 0.89 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (90 MHz) δ 79.9, 67.9, 36.9, 23.6, 20.1, 15.9, 11.5; MS (chemical ionization), m/e 133.1237 (M + 1, $C_7H_{17}O_2$ requires 133.1229), 115 (base), 97.

(2*R,3*S**,4*R**)-4-Methylhexane-2,3-diol (14):** ^{13}C NMR (90 MHz): δ 78.5, 68.5, 37.0, 25.5, 15.6, 14.7, 10.8; MS (chemical ionization), m/e 133.1235 (M + 1, $C_7H_{17}O_2$ requires 133.1229), 115 (base), 97.

(2*R,3*R**,4*S**)-4-Methylhexane-2,3-diol (15):** ^{13}C NMR (90 MHz) δ 78.8, 68.9, 36.4, 27.0, 19.4, 12.7, 11.7; MS (chemical ionization), m/e 133.1236 (M + 1, $C_7H_{17}O_2$ requires 133.1229), 115 (base), 97.

(2*R,3*S**,4*S**)-4-Methylhexane-2,3-diol (16):**[20] ^{13}C NMR (90 MHz) δ 78.2, 68.4, 36.3, 25.6, 17.0, 14.4, 11.0.

General Procedure for Additions of Crotyldicyclopentadienyltitanium(IV) Chloride to 8a–d. To dicyclopentadienyltitanium chloride[6a] (298.0 mg, 1.20 mmol) in THF (10 mL) was added slowly the crotylmagnesium chloride (0.49 M, 4.9 mL, 2.40 mmol) at room temperature under argon with stirring. The resulting orange mixture was stirred for 2 h, and the aldehyde **8a–d** (1.0 mmol) in THF (0.5 mL) was added slowly at 0 °C. The reaction mixture was raised to room temperature gradually (ca. 1 h) and then poured into a mixture of water (8 mL) and ether (25 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the extracts were combined, washed with water (3 × 8 mL) and brine (2 × 8 mL), and dried ($MgSO_4$). The excess solvents were evaporated under reduced pressure to give a crude mixture of the four diastereomeric homoallylic alcohols **9a–d**, **10a–d**, **11a–d**, and **12a–d** as thick colorless oils.

General Procedure for Additions of Crotyldicyclopentadienylzirconium(IV) Chloride 8a–d. To dicyclopentadienylzirconium chloride[7] (356.0 mg, 1.22 mmol) in THF (7.0 mL) was added slowly the crotylmagnesium chloride (0.49 M, 5.0 mL, 2.44 mmol) at room temperature under argon with stirring. The resulting orange mixture was stirred for 2 h, and the aldehyde **8a–d** (1.0 mmol) in THF (0.5 mL) was added slowly at 0 °C. After completion of the reaction, workup as before afforded the four diastereomeric homoallylic alcohols **9a–d**, **10a–d**, **11a–d**, and **12a–d** as thick colorless oils.

General Procedure for Additions of Crotyltitanium Triphenoxide to 8a–c. To triphenoxytitanium chloride[21]/THF solution (0.335 M, 3.64 mL, 1.22 mmol) and THF (5 mL) was added slowly crotylmagnesium chloride (0.49 M, 2.6 mL, 1.22 mmol) at −78 °C under argon with stirring. The resulting black mixture was stirred for 2 h at −30 °C, and the mixture then cooled to −100 °C, whereupon the aldehyde **8a–c** (1.0 mmol) in THF (0.5 mL) was added slowly. The reaction mixture was raised to room temperature gradually (ca. 2 h). After completion of the reaction, workup as before afforded the four diastereomeric homoallylic alcohols **9a–c**, **10a–c**, **11a–c**, and **12a–c** as thick colorless oils.

General Procedure for Additions of Crotylchromium(II) Chloride to 8a,e. To chromium(II) chloride[5a] (149.9 mg, 1.22 mmol) in THF (5 mL) was added slowly a degassed solution containing crotyl bromide (164.7 mg, 1.22 mmol) and the aldehyde **8a,e** (1.0 mmol) in THF (10 mL) at 0 °C with stirring. The resulting mixture was stirred for 2 h at room temperature and then quenched with water (5 mL). Workup as before afforded the diastereomeric homoallylic alcohols **9a,e** and **10a,e** as thick colorless oils.

General Procedure for Additions of Crotylchromium(II) Chloride–THF Complex to 8a,c. To $CrCl_3 \cdot (THF)_3$[22] (1.498 g, 4.00 mmol) in THF (10 mL) was added slowly crotylmagnesium chloride (0.49 M, 8.2 mL, 4.00 mmol) at −78 °C with stirring. The mixture was allowed to warm to −50 °C for 10 min and then recooled to −78 °C for 30 min. The aldehyde **8a,c** (1.00 mmol) in THF (1.0 mL) was then added at −78 °C under argon. The resulting was stirred for 12 h at room temperature and then quenched with water (5 mL). Workup as before afforded the four diastereomeric homoallylic alcohols **9a,c**, **10a,c**, **11a,c**, and **12a,c** as thick colorless oils.

General Procedure for Additions of Crotyltri-*n*-butylstannane to 8a,d. To $MgBr_2 \cdot Et_2O$ (309.9 mg, 1.20 mmol) in THF (10 mL) was added slowly the aldehyde **8a,d** (1.00 mmol) at −20 °C under argon with stirring. The mixture was stirred at −10 °C for 10 min, and crotyltri-*n*-butylstannane (414.6 mg, 1.20 mmol) was added at −78 °C. The resulting mixture was stirred for 12 h at room temperature and then quenched with water (5 mL). Workup as before (with the exception that the organic extracts were washed with saturated aqueous KF to remove organotin compounds) afforded the diastereomeric homoallylic alcohols **9a,d**

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(minor) and **11a,d** (major) as thick colorless oils.

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Supplementary Material Available: Data from single-crystal X-ray analyses of the 3,5-dinitrobenzoates esters of **9a** and **11a** (11 pages). Ordering information is given on any current masthead page.

Addition of Oxygen- and Sulfur-Centered Radicals to [1.1.1]Propellane[1]

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There is considerable current interest in the reactivity of molecules with inverted structures at carbon,[4] specially, [1.1.1]propellane.[5] Many processes, such as the additions of *tert*-butyl hypochlorite, thiols, disulfides, diselenides, biacetyl, and halogens are presumed to involve a free-radical mechanism.[6-13] While S_H2 displacements at carbon are extremely rare,[14] reaction at the bridge position in [1.1.1]propellane releases considerable strain and allows both positions with inverted structure to acquire a more favorable conformation. Thus, it is important to obtain absolute rates of radical scavenging by [1.1.1]propellane; we have carried out measurements for *tert*-butoxy and thiophenoxy radicals by use of laser flash photolysis techniques. The results of these studies are reported herein.

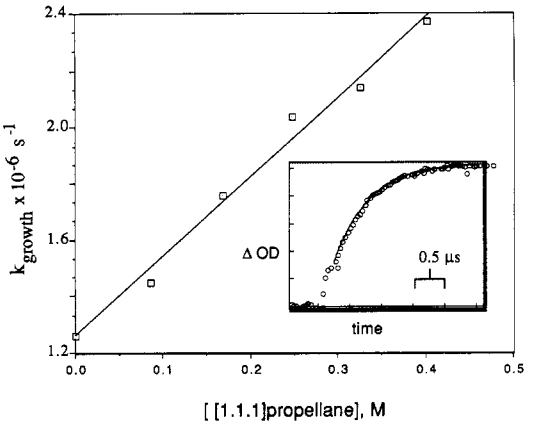

Figure 1. Plot according to eq 5 for $[Ph_2CHOH]$ = 69 mM. Insert: Transient absorption trace showing the buildup of ketyl signal at 535 nm, for 85 mM [1.1.1]propellane.

Results and Discussion

tert-Butoxy radicals do not show any significant absorptions at $\lambda > 300$ nm. It was therefore necessary to employ a probe technique that has been widely used in measurements of this type.[15] The radicals were generated by laser photolysis of di-*tert*-butyl peroxide at 337 nm. Reactions 1–4 show the mechanism proposed.

$$Bu^tOOBu^t \xrightarrow{h\nu} 2Bu^tO^\bullet \quad (1)$$

$$Bu^tO^\bullet \rightarrow \text{first-order decay} \quad (2)$$

$$Bu^tO^\bullet + Ph_2CHOH \rightarrow Bu^tOH + Ph_2\dot{C}OH \quad (3)$$

(4)

Reaction 1 generates radicals within the duration of the laser pulse with a high quantum yield.[16,17] The radicals can decay by reacting with the substrate (reaction 4) or the probe (reaction 3, $Ph_2\dot{C}OH$, λ_{max} 535 nm). In addition, $Bu^tO^\bullet$ can undergo first- and pseudo-first-order processes, such as β-cleavage or reaction with the solvent (reaction 2).[15] The buildup of the ketyl signal at 535 nm follows clean first-order kinetics (see insert in Figure 1); a monoexponential fit of the signal growth leads to k_{growth}, which is related to the rate constants of interest according to

$$k_{growth} = k_2 + k_3[Ph_2CHOH] + k_4[\text{propellane}] \quad (5)$$

Thus, a plot of k_{growth} against the concentration of [1.1.1]propellane at constant diphenylmethanol concentration yields from the slope the value of k_4. The plot of Figure 1 leads to $k_4 = (2.8 \pm 0.3) \times 10^6$ M^{-1} s^{-1} in a 1:1 (v/v) mixture of benzene:di-*tert*-butyl peroxide. This is a remarkably fast reaction, since alkoxy radicals rarely add efficiently to unsaturated systems.[18,19]

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