Synthetic Studies on the Carbomycins (Magnamycins): An Exception to the Enantioselective Synthesis of β-Alkyl Carboxylic Acids via Chiral Oxazolines

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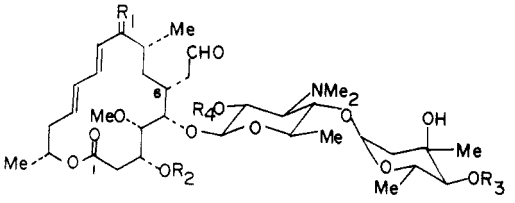
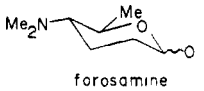
We have observed that α,β-unsaturated oxazolines **9**, bearing a β-glucose unit, when treated with allylic lithium reagents, give stereoselectivity that is opposite that predicted by Meyers' arguments. Alkyllithium reagents add in the predicted manner. Unsaturated ester **10**, when treated with lithium diallylcuprates, gives the same relative stereochemistries as are afforded by the alkyllithium reagents with oxazoline **9**. Lithium dialkylcuprates, when added to **10**, provide the stereochemistry obtained by treating oxazolines **9** with allyllithiums. Both allyllithiums and alkyllithiums add to oxazoline **15** in the manner predicted by Meyers.

The 16-membered macrolide antibiotics **1** constitute a class of clinically important compounds which are active against gram-positive bacteria and certain *Mycoplasma* strains.[2] Early degradation studies established the structures of the sugar residues and the aglycon portions of the spiramycins **1d,e** and carbomycin B (magnamycin B, **1a**).[3] The structure of leucomycin A_3 (**1b**) was defined by single-crystal X-ray analysis of demycarosylleucomycin A_3 hydrobromide[4] and was eventually correlated with the spiramycin–carbomycin series by Omura.[5]



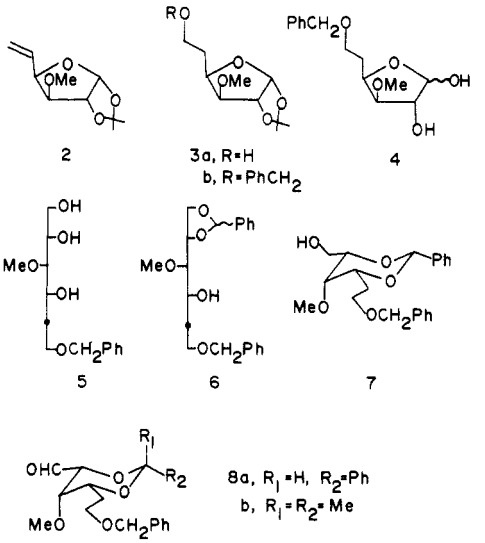
1a, R_1 = O; R_2 = Ac; R_3 = isovalerate; R_4 = H [carbomycin B (magnamycin B)]
b, R_1 = α-OH; R_2 = Ac; R_3 = isovalerate; R_4 = H (leucomycin A_3)
c, R_1 = O; R_2 = H; R_3 = isovalerate; R_4 = H (niddamycin)
d, R_1 = forosamine; R_2 = Ac; R_3 = H; R_4 = Ac (spiramycin II)
e, R_1 = forosamine; R_2 = R_3 = R_4 = H (spiramycin I)



forosamine

Tatsuta's successful attachment of the carbohydrate units to carbonolide B, the aglycon of carbomycin B,[6] and the early recognition that the absolute stereochemistry at C-3, C-4, and C-5 of carbomycin B correlated with C-4, C-3, and C-2, respectively, of D-glucose[7,8] set the stage for the total synthesis of carbomycin B by Tatsuta[9] and Nicolaou.[10]

Chart I



These successful approaches and the efforts in this laboratory have focused upon the control of the stereochemistry at C-6 by nucleophilic addition of a C-7 (C-8, C-9) unit to an α,β-unsaturated carbonyl moiety. Although we have developed a palladium-mediated carbon–carbon bond-forming ring closure which differs from the methods described[9-11] and which is currently being applied to the synthesis of carbonolide B, we choose to report at this time the results of a preliminary investigation in this area concerning the stereochemistry of conjugate additions of alkyllithium reagents to α,β-unsaturated oxazolines[12] and of dialkylcuprates to α,β-unsaturated esters.

Results and Discussion

Oxazoline **9a** was prepared from readily available olefin **2** (Chart I), which was synthesized from diacetone glucose by modified literature procedures[13] in 82% overall yield. The olefin was converted[7,8] in 85% yield to alcohol **3a** via hydroboration and alkaline peroxide oxidation. Subsequent alkylation afforded benzyl ether[8,14] (**3b**). Three

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(13) Josan, J. S.; Eastwood, F. W. *Carbohydr. Res.* **1968**, *7*, 161. The orthoformate (from trimethyl orthoformate) was first heated at 95 °C to remove benzene and excess trimethyl orthoformate, followed by heating at 150–170 °C as described.
(14) This method was adapted from the previously employed O-allylation procedure.[8] The instability of the allyl ether during the latter stages of our synthesis required the use of the benzyl ether.

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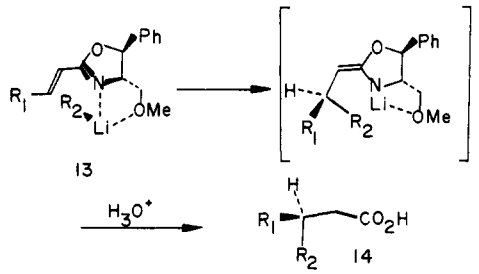
Scheme I



methods, which would provide flexibility at the required time of eventual deprotection, were found to be successful for the removal of the benzyl protecting group of **3b**. These techniques were (1) hydrogenolysis (10% Pd/C; 30 psi of H_2; ethyl acetate; 95% yield), (2) benzylic bromination and hydrolysis (NBS, $h\nu$, CCl_4, reflux; H_2O; 90% yield), and (3) oxidation with chromyl chloride in dichloromethane, followed by reductive workup with zinc (90% yield).

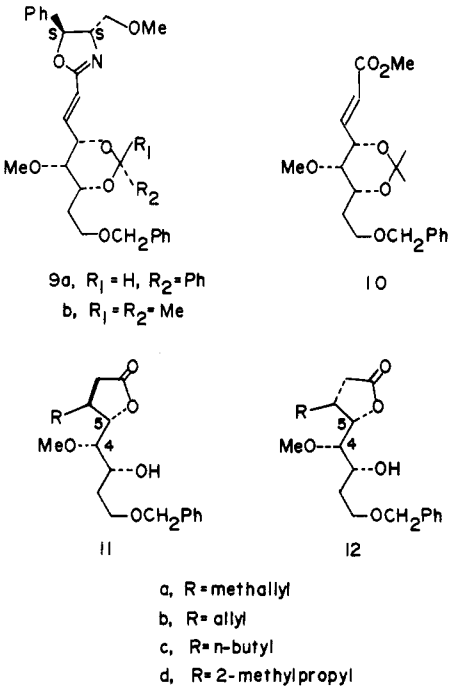
Exposure of acetonide **3b** to a refluxing mixture of dioxane and a 4% sulfuric acid solution (1:1) provided anomeric hemiacetals **4**. Reduction of these latent aldehydes with sodium borohydride in ethanol generated water-soluble triol **5**. Conversion of the borate salts in acidic methanol to trimethyl borate,[15] followed by distillation of the volatiles, obviated the need for an aqueous workup. Treatment of the crude triol with benzaldehyde under acidic conditions produced 1,3-dioxane **7a** and dioxolanes **6** in a 6:1 ratio. The axial benzylidene methine proton in **7a** resonates at δ 5.56[16] while the corresponding dioxolane protons resonate at δ 5.94 and δ 5.82 (1:1). The treatment of triol **5** with 2,2-dimethoxypropane afforded an inseparable mixture of the five- and six-membered acetonides. Similar treatment of hemiacetal **4** gave dioxolane **3b** only.

Standard Collins oxidation[17] of alcohol **7** produced the functionalized D-glucose **8a** in moderate yields (40–50%) due to facile elimination of the axial methoxy group. The introduction of acetic anhydride to the reaction mixture, according to the procedure of Garegg and Samuelsson,[18] raised the yield of **8a** to 90%. This modification buffers the reaction mixture and facilitates the interconversion of chromium among its various oxidation states.

Meyers has reported[19] the stereoselective conjugate addition of alkyllithium reagents to chiral *E* α,β-unsaturated oxazolines **13**. Subsequent hydrolysis afforded 3-alkanoic acids **14** (Scheme I) in 95–99% enantiomeric excesses. An appropriate organolithium reagent containing the C-7, C-8, and C-9 centers and the C-8 methyl group of carbomycin B could be employed in this context to give the correct stereochemistry at C-6.

The condensation of aldehyde **8a** with (–)-(4*S*,5*S*)-2-((diethylphosphono)methyl)-4-methoxy-5-phenyl-2-oxazoline, in analogy with Meyers' procedure,[12] generated (*E*)-oxazoline **9a** (see Chart II). The use of the prescribed diisopropyl phosphonate gave a lower isolated yield of (*E*)-oxazoline **9a** (41% yield vs. 25% yield) although the *E*/*Z* ratio was greater for the diisopropyl reagent (12/1 vs. 4/3).

Chart II[a]



[a] R_1 = Me, Et, *i*-Pr, cyclohexyl, $MeOCH_2CH_2$, Ph; R_2 = Et, *n*-Pr, *n*-Bu, Ph.

The potential availability of (*R*)-3-(benzyloxy)-2-methylpropyllithium[20] as the required organolithium reagent prompted an investigation of the reactivity of the racemic reagent toward (*E*)-oxazoline **9a**. This reagent did not add to the oxazoline at –78 °C, presumably due to intramolecular coordination of the lithium and oxygen atoms. Kishi[21] has reported the formation of the Grignard reagent of (*R*)-1-bromo-2-methyl-3-butene. However, attempts to prepare the corresponding lithium reagent from the racemic halides by reductive methods were unsuccessful.

Methallyllithium underwent conjugate addition (–78 °C) to provide an adduct, which, after hydrolysis with aqueous methanolic sulfuric acid, gave rise to a 95/5 mixture of five-membered lactones (1773 cm^{-1}). The 270-MHz NMR spectrum of the lactones revealed the C-4 methine proton of the major component as a doublet of doublets at δ 3.17 ($J_{3,4}$ = 4.8 Hz, $J_{4,5}$ = 3.3 Hz) while the lactone methine proton at C-5 appeared as a doublet of doublets at δ 4.40 ($J_{4,5}$ = 3.3 Hz, $J_{5,6}$ = 4.4 Hz). This lactone proved to be the trans isomer **11a**. Lactone **12a**, which has been prepared by Nicolaou by the addition of lithium dimethallylcuprate to unsaturated ester **10**[10,22] followed by hydrolysis, although having a similar 270-MHz NMR spectrum to that of lactone **11a**, displayed its C-5 proton downfield at δ 4.70 (dd, $J_{4,5}$ = 3.8 Hz, $J_{5,6}$ = 7.0 Hz) between the vinyl proton signals and the C-4 methine proton downfield at δ 3.34 (t, $J_{3,4}$ = 3.7 Hz) relative to its counterpart in **11a**. Careful examination of the 270-MHz NMR spectrum of lactone **11** revealed the presence of 5% of the cis isomer **12a**. The C-5 methine proton of trans-substituted 4,5-dialkyl-2(3*H*)furanones generally absorb at higher field than their cis counterparts.[23] Moreover,

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(22) We are grateful to Professor K. C. Nicolaou, University of Pennsylvania, for providing us with the experimental details for this transformation.

Table I. Relative Yields and 270-MHz NMR Data for Lactones 11 and 12

entry	RM[b]	substrate	11/12 (trans/cis) ratio	chemical shift,[a] δ C_4H	chemical shift,[a] δ C_5H
1	MeAyLi	9a	95/5	3.17 (dd, J = 4.8, 3.3 Hz)	4.40 (dd, J = 4.4, 3.3 Hz)
2	MeAyLi	9b	90/10	same as entry 1	
3	AyLi	9a	95/5	3.17 (dd, J = 4.8, 3.3 Hz)	4.42 (dd, J = 4.8, 3.3 Hz)
4	n-BuLi	9a	1/99	3.30 (dd, J = 4.0, 3.0 Hz)	4.73 (dd, J = 6.9, 2.8 Hz)
5	2-MePrLi	9a	7/93	3.28 (dd, J = 4.1, 2.8 Hz)	4.69 (dd, J = 6.9, 2.8 Hz)
6	$(MeAy)_2CuLi$	10	7/93	3.34 (t, J = 3.8 Hz)	4.70 (dd, J = 7.0, 3.8 Hz)
7	n-Bu_2CuLi	10	99/1	3.17 (t, J = 3.6 Hz)	4.38 (dd, J = 6.4, 3.6 Hz)

[a] The values represent data for the major component. [b] Ay = allyl, MeAy = methallyl.

lactone **12a** has been successfully relayed to carbomycin B and the lithium aluminum hydride-derived triol of **12a** has been subjected to single-crystal X-ray analysis.[10]

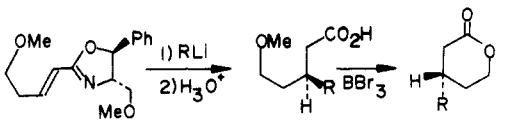
We sought to explore the nature of this discrepancy by varying such parameters as the acetal, the organolithium reagent (with the unsaturated oxazolines), or the cuprate (with unsaturated esters). The stereochemical analysis of the conjugate addition products was based upon integration of the C-5 methine proton in **11** and **12**.

Oxazoline **9b** was not accessible though the acetonide **8b**, since, as previously noted, the triol **5** gave an inseparable mixture of acetonide derivatives. Ozonolysis of ester **10**[10] provided **8b**, which was converted to oxazoline **9b** by the phosphonate route. Entries 1 and 2 (Table I) show virtually no difference in selectivity between the benzylideneoxazoline **9a** and the acetonide oxazoline **9b**, and this implies no influence by the acetal unit in controlling stereoselectivity.

Allyllithium (entry 3) also gives the trans lactone selectively. However, n-butyllithium undergoes a clean reversal of stereochemistry as does the branched alkyllithium of entry 5. The selectivity observed with allyllithiums and alkyllithiums is reversed when their derived cuprates undergo conjugate addition to the unsaturated esters. Thus, lithium dimethallylcuprate (entry 6) provides preferentially the cis lactone (Nicolaou route) while the trans lactone is the major stereoisomer produced when lithium di-n-butylcuprate is employed. It is apparent from these data that subtle effects are operative, and no simple analysis of reactive transition-state conformations of the substrate could have predicted a priori the eventual outcome of these reactions.

The oxazoline **15** (Table II) was prepared[12] to assess the effect of the glucose residue on the stereochemical control. This substrate was chosen because a single oxygen atom replaced the highly oxygenated glucose unit. Entries 3 and 4 indicate that the stereochemistries of addition of allyllithium to **15** is the same as is observed for n-propyl- and n-butyllithium. The addition of allyllithium proceeds according to Meyers' predictions. However, a solvent dependence was observed. When allyllithium was prepared from allyltriphenyltin with commercial phenyllithium (Alfa-Ventron) containing benzene (entry 3), the rotation of the valerolactone **16a** (after reduction of the double bond) was less than when the phenyllithium was prepared from bromobenzene and n-butyllithium in the absence of benzene (entry 4). When oxazoline **15** was treated with n-propyl- or n-butyllithium in the presence of benzene (25% of the final reaction volume), the rotations of the valerolactones **16a** (entry 2) and **16b** (entry 6) dropped comparably. This solvent dependence was also observed in the reaction of methallyllithium with (*E*)-oxazoline **9a** (90/10, without benzene).

Table II. Optical Data for Lactones 16



15 16a, R = n-propyl; b, R = n-butyl

entry	R	overall yield, %	$[\alpha]^{25}_D$, deg	optical yield, %
1	n-propyl[b]	24	−23.9 (c 8.9, $CHCl_3$)	95
2	n-propyl (+ benzene)	23	−19.0 (c 4.4, $CHCl_3$)	76
3	allyl[a]	20	−18.0 (c 3.8, $CHCl_3$)	72
4	allyl (− benzene)[a]	21	−22.1 (c 2.9, $CHCl_3$)	88
5	n-butyl[b]	30	−22.3 (c 9.0, $CHCl_3$)	95
6	n-butyl (+ benzene)	29	−19.0 (c 3.6, $CHCl_3$)	81

[a] Addition product hydrogenated (PtO_2, EtOH) prior to hydrolysis. [b] Repetition and confirmation of ref 12. The concentrations were approximately half those employed by Meyers and the temperature of the measurements was 2 °C higher. The rotation values are fortuitously the same as those reported. The percent enantiomeric excess is computed from the literature values.

In summary, these data demonstrate that in the case of monoether oxazoline **15**, the oxazoline controls stereoselectivity with either allylic or unstabilized alkyllithiums. In the case of oxazolines **9**, which bear the glucose unit, a clear distinction is made between the two types of organolithium reagents. The glucose unit clearly plays a role in this process. Whether it is in tandem with or exclusive of the oxazoline unit cannot be answered in the context of these data. It is known that n-butyllithium is tetrameric at both 25 and −78 °C in THF[24] and that allyllithium exists in a stacked array with a degree of aggregation greater than 1.4 at 25 °C in THF.[25] It is premature to put forth a meaningful interpretation of these data until a better appreciation of aggregation state, chelation, and reactive conformations can be obtained. However, these results

(23) We express our appreciation to Professor P. A. Bartlett, University of California at Berkeley, for providing us, prior to publication, with NMR data on a number of 4,5-disubstituted 3*H*-furan-2-ones.

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serve as a caveat for the application of enantioselective methods where more than one controlling element may be present.

Experimental Section

Melting points were obtained on a Fisher-Jones apparatus and are corrected. Boiling points are uncorrected. Combustion analyses were performed by Atlantic Microlabs or by Dr. Rittner and Mr. Giunta of Olin Corp.

Infrared spectra were recorded by using either a Beckman Model 4250 spectrometer or a Nicolet Model 7199 Fourier transform spectrometer with 4-cm^{-1} resolution. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-32 (90 MHz), a JEOL FX90Q (90 MHz), or a Bruker HX-270 (270 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from a tetramethylsilane internal standard. Gas chromatography was performed on a Varian Model 1400 thermal gas chromatograph, equipped with a 1.5% OV-101 (Anakrom) column (8 ft × $^1/_8$ in., helium carrier gas, flow rate 30 mL/min). Mass spectra were recorded on a Hewlett-Packard Model 5895 gas chromatograph–mass spectrometer system, equipped with a 3% OV-101 column (2 ft × $^1/_8$ in., helium carrier gas). Solid samples were analyzed by using a direct-insertion probe. Peaks greater than 10% of the base peak exclusive of the molecular ion are reported. Optical rotations were measured on a Perkin-Elmer Model 241 automatic polarimeter.

Solvents and reagents were used as received unless otherwise noted. Purification of such compounds, when necessary, followed the general procedures outlined by Perrin et al.[26] Tetrahydrofuran (THF), diethyl ether, 1,2-dimethoxyethane (DME), pentane, and toluene were dried by refluxing these solvents over sodium benzophenone ketyl, followed by distillation. Pyridine, triethylamine, diisopropylamine, and *N,N*-dimethylformamide were distilled from calcium hydride under a nitrogen atmosphere. Dichloromethane was distilled from phosphorus pentoxide.

All glassware was flame dried under a continuous stream of nitrogen for reactions requiring anhydrous conditions. Magnetic stirrers were used unless otherwise noted.

Flash chromatography was performed according to the procedure of Still[27] by using silica gel (particle size 0.040–0.063 nm, 234–400 mesh ASTM, EM Reagents). Thin-layer chromatography (TLC) was used to analyze the collected fractions; TLC plates were developed with ultraviolet light, a 2,4-dinitrophenylhydrazine spray, concentrated sulfuric acid spray, or an iodine chamber.

High-pressure liquid chromatography was performed on a Waters Prep LC 500 instrument by using the following parameters: flow rate, 1.5 L/min; solvent pressure, 4–6 atm; chamber pressure, 25–30 atm; silica gel cartridges.

(−)-5-Deoxy-1,2-di-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose (3a). Dry tetrahydrofuran (150 mL) was cooled to 0 °C under a nitrogen atmosphere, and 2-methyl-2-butene (117 mL, 1.1 mol) was added in one portion. Borane–dimethyl sulfide complex (52.3 mL, 0.55 mol) was added dropwise with a syringe such that the internal temperature did not exceed 10 °C. The reaction mixture was then stirred at 0–5 °C for 2.0 h. A solution of olefin 2[13] (100 g, 0.5 mol) in dry tetrahydrofuran (550 mL) was added via an addition funnel so that the internal temperature did not exceed 10 °C. After the addition was complete, the clear, colorless reaction mixture was warmed gradually to 25 °C and stirred for 18.5 h. The reaction mixture was cooled to 0–5 °C. A mixture of a 30% hydrogen peroxide solution (212 mL, 1.92 mol) and a 3 N sodium hydroxide solution (960 mL, 2.88 mol) was added slowly so that the internal temperature did not exceed 20 °C. After the addition was complete, the reaction mixture was warmed slowly to 25 °C and stirred for 2.0 h. After the mixture was cooled to 5 °C, solid sodium sulfite was added (mild exotherm) until saturation occurred and the solution gave a negative starch–iodide test. The layers were separated, and the organic layer was concentrated in vacuo. The aqueous layer was extracted with ether three times, and the combined concentrate and ether washings were washed twice with water, dried over magnesium sulfate, filtered, and concentrated in vacuo.

Vacuum distillation gave 91 g (83% yield) of a clear, colorless liquid: bp 110 °C (0.25 mmHg); IR (neat) 3450 (br, s), 2950 (s), 2830 (s), 1470 (s), 1375 (s), 1300 (m), 1150 (m), 940 (s), 870 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 5.89 (d, 1 H, J = 3.8 Hz), 4.59 (d, 1 H, J = 3.9 Hz), 4.32 (ddd, 1 H, J = 8.4, 5.0, 3.4 Hz), 3.79–3.74 (m, 2 H), 3.62 (d, 1 H, J = 2.9 Hz), 3.42 (s, 3 H), 2.65 (m, 1 H, concentration dependent), 2.06–1.81 (m, 2 H), 1.50 (s, 3 H), 1.33 (s, 3 H); $[\alpha]^{31}_D$ −47.6° (*c* 1.0, $CHCl_3$) [lit.[7] $[\alpha]^{23}_D$ −44.53° (CH_3OH)].

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.92; H, 8.31.

(−)-5-Deoxy-6-*O*-benzyl-1,2-di-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose (3b). Sodium hydride (60% in oil, 4.4 g, 110 mmol) was washed three times with dry pentane under a nitrogen atmosphere in a flame-dried flask. After evaporation of residual pentane under a stream of nitrogen, dry tetrahydrofuran (150 mL) was added via a syringe. Alcohol **3a** (20.0 g, 91.6 mmol) in 50 mL of dry tetrahydrofuran was added, and the resulting suspension was refluxed for 1 h. After the mixture was cooled to 25 °C, benzyl bromide (16.1 g, 11.2 mL, 94 mmol) was added in three portions. The reaction mixture was then stirred at 25 °C for 17.5 h. The reaction mixture was quenched with methanol, and the tan suspension was diluted threefold with ether and washed twice with water. The combined aqueous layers were back-extracted twice with 20 mL of ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. Vacuum distillation gave 26.0 g (93%) of a clear, pale yellow liquid: bp 155 °C (0.1 mmHg); FT IR (neat) 3089 (m), 3063 (m), 3031 (m), 2986 (s), 2932 (s), 2867 (s), 2832 (s), 1497 (m), 1454 (m), 1383 (s), 1374 (s), 1312 (m), 1297 (m), 1259 (s), 1215 (s), 1194 (s), 1166 (s), 1090 (s), 1019 (s), 886 (s), 862 (s), 852 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.43–7.22 (m, 5 H), 5.86 (s, 1 H, J = 4 Hz), 4.65 (d, 1 H, J = 4 Hz), 4.56 (s, 1 H), 4.54 (s, 1 H), 4.33 (td, 1 H, J = 7 Hz), 3.60 (t, 2 H, J = 6 Hz), 3.56 (t, 1 H, J = 3 Hz), 3.34 (s, 3 H), 2.11–1.90 (m, 2 H), 1.49 (s, 3 H), 1.31 (s, 3 H); GC/MS (70 eV, column temperature 200 °C), *m/e* (relative intensity) 308 (M^+, 0.3), 163 (10.7), 92 (10.3), 91 (100), 87 (39.0), 85 (30.1), 73 (14.2), 71 (23.7), 65 (12.6), 59 (18.9), 58 (17.5); $[\alpha]^{29}_D$ −34.9° (*c* 2.3, $CHCl_3$).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.34; H, 7.91%.

6-*O*-Benzyl-5-deoxy-3-*O*-methyl-D-glucofuranose (4). To a solution of benzyl ether **3b** (20.0 g, 64.6 mmol) dissolved in 200 mL of reagent grade dioxane was added a 4% sulfuric acid solution (200 mL), and the resulting translucent mixture was stirred at reflux for 2 h under a nitrogen atmosphere. The clear, pale yellow reaction mixture was cooled to 25 °C and carefully neutralized with solid sodium carbonate. The layers were separated, and the aqueous layer was extracted with dioxane (25 mL). The organic solvent was removed on a rotary evaporator, and the orange-yellow residue was taken up in ether. The layers were separated, and the aqueous layer was extracted twice with ether. The organic solution was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give crude hemiacetal **4** as a viscous, clear, pale yellow liquid (17.4 g, 100% crude yield) which was a 3:1 mixture of anomers: FT IR (neat) 3385 (s, br), 3087 (s), 3065 (s), 3030 (s), 2929 (s), 1605 (m), 1587 (m), 1498 (s), 1455 (s), 1364 (s), 1269 (s), 1256 (s), 1204 (s), 1074 (s, br), 951 (s), 872 (s), 807 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.44–7.22 (m, 5 H), 5.43–5.36 (br s, 0.75 H), 5.07 (br d, 0.25 H, J = 10 Hz), 4.77–4.63 (m, 1 H), 4.61–4.14 (m, 2 H), 4.55 (s, 2 H), 4.08–3.80 (m, 2 H, concentration dependent), 3.50–3.46 (m, 2 H), 3.35 (s, 3 H), 2.07–1.77 (m, 2 H).

6-*O*-Benzyl-5-deoxy-3-*O*-methyl-D-glucitol (5). The crude anomeric hemiacetals **4** (17.4 g, 64.6 mmol) were dissolved in 255 mL of absolute ethanol. Sodium borohydride (12.2 g, 320 mmol) was added, and the reaction mixture was stirred under a nitrogen atmosphere at room temperature for 72 h. Solvent was removed on a rotary evaporator, and the borate salts were immediately dissolved in 600 mL of methanol. Dowex 50W-X8 (H^+) resin (J. T. Baker Chemical Co.) was added with mechanical stirring until the solution was approximately pH 5 (wet pH paper). After the mixture was stirred for 30 min, the resin was filtered and washed with methanol. Solvent was removed from the filtrate on a rotary evaporator, and the deep yellow oil was taken up in 200 mL methylene chloride. The organic solution was dried over anhydrous sodium sulfate and filtered. Solvent was removed in

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

vacuo to give the crude triol as a yellow syrup: 16.1 g (92% crude yield); IR (neat) 3358 (s, br), 3075 (m), 3050 (m), 3025 (m), 2925 (s), 1608 (w), 1490 (s), 1455 (s), 1410 (s), 1360 (s), 1305 (s), 1200 (s), 1075 cm^{-1} (s, br); NMR ($CDCl_3$, 90 MHz) 7.45–7.25 (m, 5 H), 4.55 (s, 2 H), 4.2–3.35 (m, 6 H), 3.50 (s, 3 H), 3.15 (m, 1 H), 2.80 (br s, 3 H, concentration dependent), 2.10–1.80 (m, 2 H).

(+)-5-Deoxy-6-*O*-benzyl-2,4-di-*O*-benzylidene-3-*O*-methyl-D-glucitol (7). To a solution of crude triol **5** (16.1 g, 59.6 mmol) dissolved in 300 mL of CH_2Cl_2 under N_2 were added 25 g of molecular sieves (flame dried in vacuo, 4 Å), freshly distilled benzaldehyde (7.1 g, 65.5 mmol), and 0.25 mL of H_2SO_4, followed by stirring for 46 h. Solid sodium carbonate was added to neutralize the mixture. After filtration through Celite, the solvent was concentrated to give a yellow oil. Flash chromatography (ether) gave three products; the first of which was benzaldehyde (R_f 0.65, ether).

Evaporation of solvent from the second fraction gave 5-deoxy-6-*O*-benzyl-1,2-di-*O*-benzylidene-3-*O*-methyl-D-glucitol (**6**), a clear yellow syrup, as a 1:1 mixture of epimeric acetals; R_f 0.34; 2.29 g (10% overall yield from acetonide **3b**); FT IR (neat) 3475 (s), 3088 (m), 3063 (m), 3031 (m), 2932 (s), 2867 (s), 1600 (m), 1584 (m), 1495 (m), 1455 (s), 1398 (s), 1362 (s), 1312 (s), 1294 (m), 1209 (s), 1094 (s), 1028 (s), 748 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.54–7.18 (m, 10 H), 5.94 (s, 0.5 H), 5.82 (s, 0.5 H), 4.65–4.30 (m, 3 H), 4.14–3.32 (m, 6 H), 3.58 and 3.56 (2 s, 3 H), 3.07–2.74 (m, 1 H), 2.31–1.71 (m, 2 H).

Evaporation of solvent from the third fraction gave glucitol **7** as a white amorphous solid: R_f 0.22; 13.4 g (58% overall yield from acetonide **3b**); mp 100–101 °C; FT IR (CCl_4) 3867 (w), 3751 (m), 3533 (w), 2955 (s), 2892 (s), 2810 (m), 1610 (w), 1481 (m), 1423 (s), 1391 (m), 1355 (m), 1286 (s), 1249 (s), 1094 (m), 1027 (m), 908 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.51–7.21 (m, 10 H), 5.56 (s, 1 H), 4.53 (s, 1 H), 4.52 (s, 1 H), 4.09–3.91 (m, 2 H), 3.83–3.47 (m, 4 H), 3.54 (s, 3 H), 3.05 (s, 1 H), 2.37–2.25 (m, 1 H, concentration dependent), 2.22–2.08 (m, 1 H), 1.99–1.84 (m, 1 H); $[\alpha]^{26}_D$ +52.8° (*c* 1.46, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.22; H, 7.34.

5-Deoxy-6-*O*-benzyl-2,4-di-*O*-benzylidene-3-*O*-methyl-D-(+)-glucose (8a). Chromium trioxide (5.6 g, 5.6 mmol; dried in vacuo over phosphorus pentoxide at 120 °C for 12 h) was added in one portion to a vigorously stirred solution of dry pyridine (9 mL, 112 mmol) in dry dichloromethane (440 mL). After 20 min, a solution of alcohol **7** (5.0 g, 14 mmol) was added in one portion, followed immediately by acetic anhydride (5.4 mL, 56 mmol). The reaction mixture changed color from deep burgundy to dark brown. After being stirred vigorously for 20 min, the reaction mixture was poured into an equal volume of ethyl acetate. The tarry residue remaining in the flask was thoroughly washed with ethyl acetate. The organic suspension with its precipitated chromium satls was filtered through a silica gel column. The clear, colorless eluant was concentrated to a clear pale yellow oil, which was dissolved in 200 mL of methylene chloride and washed twice with water. The organic liquid was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 5.0 g (99%) of a white amorphous solid. An analytically pure sample was obtained by flash chromatography [ethyl acetate (R_f 0.7) or ethyl acetate–hexanes (3:1; R_f 0.55)]: mp 96–97 °C; FT IR ($CHCl_3$) 3090 (w), 3067 (w), 3032 (w), 3011 (m), 2935 (s), 2867 (s), 2841 (m), 1737 (s), 1653 (m), 1496 (m), 1454 (s), 1405 (m), 1360 (s), 1152 (s), 1094 (s), 1028 (s), 778 (s), 760 (s), 735 cm^{-1} (m); NMR (270 MHz, $CDCl_3$) 9.75 (s, 1 H), 7.57–7.27 (m, 10 H), 5.62 (s, 1 H), 4.68–4.64 (m, 3 H), 4.30–4.29 (m, 1 H), 3.76–3.32 (m, 3 H), 3.41 (s, 3 H), 2.22–1.86 (m, 2 H); $[\alpha]^{25}_D$ +74.5° (*c* 1.17, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.72; H, 6.68.

(−)-(4*S*,5*S*)-2-((Diethylphosphono)methyl)-4-(methoxymethyl)-5-phenyl-2-oxazoline. A solution of 6.5 mL (48.8 mmol) of dry diisopropylamine in 75 mL of dry THF under N_2 at 0 °C was treated dropwise via syringe with a solution of 20.3 mL (2.4 M in hexane, 48.8 mmol) of *n*-butyllithium. After being stirred for 20 min at 0 °C, the clear pale yellow solution was cooled to −78 °C. A solution of (−)-(4*S*,5*S*)-2-methyl-4-(methoxymethyl)-5-phenyl-2-oxazoline (5.0 g, 24.4 mmol)[12] in 15 mL dry tetrahydrofuran was added dropwise via a syringe. A small amount of oxazoline freezes out of solution, but this dissolves as the reaction proceeds. After the mixture was stirred at −78 °C for 2.0 h, freshly distilled diethyl chlorophosphate (4.2 g, 3.5 mL, 24.6 mmol) was injected slowly into the reaction mixture via a syringe. After the addition was complete, the clear, deep yellow solution was warmed to 25 °C and stirred for 27 h. The reaction mixture was then poured into 100 mL water and extracted with ether (3 × 70 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give a clear, dark yellow liquid. Flash chromatography (chloroform–methanol, 97.5:2.5) gave two products: starting oxazoline (1.1 g, 21% yield; R_f 0.45) and phosphonooxazoline (5.5 g, 68% yield; R_f 0.25). The phosphonate is hygroscopic and must be stored under nitrogen at 0 °C.

An analytical sample was obtained by vacuum distillation: bp 160 °C (0.01 mmHg); IR (neat) 3060 (w), 3020 (w), 2975 (s), 2930 (s), 2820 (w), 1660 (s), 1490 (m), 1475 (m), 1450 (s), 1290 (s), 1270 (m), 1215 (m), 1190 (m), 1160 (s), 1115 (s), 1090 (m), 1060 (s), 1025 (s), 950 (s), 920 (s), 865 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.38–7.26 (m, 5 H), 5.36 (d, 1 H, J = 7 Hz), 4.24–4.13 (m, 5 H), 3.62 (dd, 1 H, J = 9.7, 4 Hz), 3.53 (dd, 1 H, J = 10 Hz, 6 Hz), 3.41 (s, 3 H), 3.05 (dd, 2 H, J = 22, 8 Hz), 1.33, 1.32 (2 t, 6 H, J = 7 Hz); $[\alpha]^{25}_D$ −30.7° (*c* 1.11, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}NO_5P$: C, 56.30; H, 7.09; N, 4.10. Found: C, 56.12; H, 7.24; N, 4.15.

(+)-(5*S*,4*S*)-2-[(3*S*,4*R*,5*S*)-7-(Benzyloxy)-5,3-(benzylidenedioxy)-4-methoxy-(*E*)-1-heptenyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline (9a). Sodium hydride (61.4% in oil, 0.06 g, 1.54 mmol) was washed with three portions dry pentane in a flame-dried flask under a nitrogen atmosphere. After the last washing, dry 1,2-dimethoxyethane (3 mL) was added. Phosphonooxazoline (vide supra; 0.508 g, 1.54 mmol) was added via syringe. Vigorous gas evolution ensued. The reaction mixture was stirred at ambient temperature until the gas evolution ceased (approximately 70 min). The cloudy orange solution was cooled to 0 °C in an ice–water bath. Aldehyde **8a** (0.500 g, 1.40 mmol) was dissolved in dry dimethoxyethane (10 mL) and added dropwise through an additional funnel over 45 min. After the addition was complete, the reaction mixture was stirred at 0 °C for 4 h. The clear orange-yellow solution was poured into a 5% sodium bicarbonate solution 15 mL) and extracted with ether (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give a yellow oil. Flash chromatography (ethyl acetate–hexanes, 3:1) gave two products after the solvent was removed. (1) (*Z*)-Oxazoline: clear yellow oil; 0.23 g (30% yield); R_f 0.37; FT IR ($CHCl_3$) 3089 (m), 3067 (m), 3036 (m), 2984 (m), 2929 (s), 2877 (s), 2830 (s), 1724 (s), 1678 (s), 1616 (s), 1496 (m), 1454 (s), 1403 (m), 1355 (s), 1331 (s), 1313 (s), 1273 (s), 1246 (m), 1215 (m), 1191 (m), 1158 (s), 1129 (s), 1100 (s), 1028 (s), 984 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.54–7.20 (m, 15 H), 6.50 (dd, 1 H, J = 12, 2 Hz), 6.13 (d, 1 H, J = 12 Hz), 5.65 (s, 0.5 H), 5.58 (s, 0.5 H), 5.47–5.33 (m, 1 H), 4.61–4.48 (m, 3 H), 4.28–3.33 (m, 3 H), 3.67 (s, 3 H), 3.41 (s, 3 H), 3.11 (s, 1 H), 2.25–2.09 (m, 1 H), 2.02–1.81 (m, 1 H). (2) (*E*)-Oxazoline **9a**: clear, pale yellow viscous oil; 0.31 g (41% yield); R_f 0.28; FT IR (CCl_4) 3089 (m), 3067 (m), 3036 (m), 2984 (m), 2929 (s), 2877 (s), 2830 (s), 1678 (s), 1616 (s), 1496 (m), 1454 (s), 1403 (m), 1355 (s), 1331 (m), 1313 (s), 1273 (s), 1246 (m), 1215 (m), 1191 (m), 1158 (s), 1129 (s), 1100 (s), 1028 (s), 984 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.59–7.22 (m, 15 H), 6.85 (dd, 1 H, J = 16 Hz, 4 Hz), 6.53 (d, 1 H, J = 16 Hz), 5.64 (s, 1 H), 5.35 (d, 1 H, J = 7 Hz), 4.61–4.47 (m, 3 H), 4.28–4.10 (m, 1 H), 3.78–3.35 (m, 4 H), 3.46 (s, 3 H), 3.40 (s, 3 H), 3.10 (s, 1 H), 2.55–2.08 (m, 1 H), 2.01–1.83 (m, 2 H); $[\alpha]^{25}_D$ +48.7 (*c* 5.17, $CHCl_3$).

Anal. Calcd for $C_{33}H_{37}NO_6$: C, 72.91; H, 6.86; N, 2.58. Found: C, 73.18; H, 6.91; N, 2.55.

(−)-(4*S*,5*S*)-2-[(2*S*,3*S*,4*R*,5*S*)-7-(Benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-(2-methylprop-2-enyl)heptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline. Methallyltriphenyltin[28] (8.28 g, 20.4 mmol) was dissolved in 80 mL of dry ether under a nitrogen atmosphere. A solution of phenyllithium [2.2 M, benzene–ether (70:30), 9.3 mL, 20.4 mmol] was added in one portion with vigorous stirring. After 30 min, the precipitate was allowed to settle, and the supernatant was transferred by syringe

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to another dry flask. The precipitate was washed with 10 mL of dry ether, and the washing was transferred as above. The alkyllithium solution was concentrated to approximately 10 mL under a stream of nitrogen with gentle heating. Dry tetrahydrofuran (20 mL) was added, and the deep red solution was cooled immediately to −78 °C. A solution of *trans*-oxazoline **9a** (1.11 g, 2.0 mmol) in dry THF (25 mL) was added dropwise via an addition funnel over 2 h. The cloudy orange reaction mixture was then stirred at −78 °C for 3 h. The organic liquid was poured into a 5% sodium bicarbonate solution and extracted three times with ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give a yellow oil containing some white solid.

Flash chromatography (ether) gave two products after removal of solvent. (1) Methallyltriphenyltin: 0.10 g; R_f 0.7. (2) The desired oxazoline: clear, pale yellow oil; R_f 0.45; 0.66 g (56% yield); FT IR ($CHCl_3$) 3069 (m), 3035 (m), 2940 (s), 2886 (m), 1664 (s), 1496 (m), 1454 (s), 1406 (s), 1353 (s), 1288 (m), 1249 (m), 1197 (s), 1167 (s), 1155 (s), 1128 (s), 1098 (s), 1029 (m), 986 (m), 894 cm^{-1} (m); NMR ($CDCl_3$, 270 MHz) 7.64–7.21 (m, 15 H), 5.52 (s, 1 H), 5.24 (d, 1 H, J = 6.6 Hz), 4.88 (s, 1 H), 4.81 (s, 1 H), 4.54 (d, 1 H, J = 4.0 Hz), 4.18–3.96 (m, 3 H), 3.81–3.23 (m, 5 H), 3.58 (s, 3 H), 3.23 (s, 3 H), 3.16 (s, 1 H), 2.88–2.45 (m, 3 H), 2.36–1.87 (m, 4 H), 1.76 (s, 3 H); $[\alpha]^{25}_D$ −7.3° (*c* 5.61, $CHCl_3$).

Anal. Calcd for $C_{37}H_{45}NO_6$: C, 74.09; H, 7.56; N, 2.34. Found: C, 73.81; H, 7.34; N, 2.51.

(+)-(4*S*,5*S*)-4-(2-Methyl-2-propenyl)-5-[(1*S*,2*R*)-4-(benzyloxy)-2-hydroxy-1-methoxybutyl]dihydrofuran-2(3*H*)-one (11a). The aforementioned oxazoline (1.15 g, 1.92 mmol) was dissolved in absolute methanol (45 mL). A 20% sulfuric acid solution (15 mL) was added, and the turbid reaction mixture was stirred at 25 °C for 24 h. The resulting clear yellow solution was saturated with sodium chloride and extracted three times with ether. The combined organic layers were dried over sodium carbonate and magnesium sulfate, filtered, and concentrated in vacuo to afford a yellow oil. Flash chromatography (ether) gave two products after the removal of solvent. (1) Benzaldehyde, R_f 0.7. (2) Lactone **11a**: clear, pale yellow oil; R_f 0.28; 0.44 g (67% yield); FT IR ($CHCl_3$) 3494 (s), 3077 (m), 3033 (m), 2977 (s), 2935 (s), 2871 (s), 1773 (s), 1650 (m), 1495 (m), 1456 (s), 1446 (s), 1420 (s), 1383 (s), 1363 (s), 1181 (s), 1104 (s), 1026 (s), 928 (s), 909 (s), 898 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.37–7.23 (m, 5 H), 4.81 (s, 1 H), 4.76 (dd, 0.05 H, J = 7.6, 4 Hz), 4.70 (s, 1 H), 4.50 (s, 2 H), 4.39 (dd, J = 4, 0.95 H), 4.02–3.97 (m, 1 H), 3.76–3.60 (m, 2 H), 3.53 (s, 3 H), 3.19–3.10 (m, 2 H), 2.86–2.54 (m, 2 H), 2.30–1.77 (m, 5 H), 1.70 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) 176.5, 141.9, 137.7, 128.2, 127.5, 112.8, 85.1 (5%), 84.8 (5%), 83.5 (95%), 73.1, 70.0 (95%), 69.5 (5%), 68.5 (95%), 67.6 (5%), 60.5, 42.1, 34.7 (95%), 34.2 (95%), 33.7 (5%), 33.3 (5%), 32.6, 21.9, 21.7; $[\alpha]^{26}_D$ +27.2° (*c* 1.22, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.19; H, 8.02.

Extraction of the silica gel column with methanol removed material at the origin. Removal of solvent gave 0.05 g of crude yellow oxazolinediol: FT IR ($CHCl_3$) 3362 (s), 3068 (s), 3033 (s), 2932 (s), 1657 (s), 1496 (s), 1451 (s), 1408 (s), 1378 (s), 1352 (s), 1102 cm^{-1} (s); NMR ($CDCl_3$, 90 MHz) 7.4–7.1 (m, 10 H), 5.4 (d, J = 3 Hz, 1 H), 4.9–4.7 (m, 2 H), 4.5 (s, 2 H), 3.8–3.1 (m, 8 H), 3.7 (s, 3 H), 3.5 (s, 3 H), 2.2–1.6 (m, 12 H). This material could be recycled to afford lactone **11a**.

(+)-(4*S*,5*S*)-2-[(2*S*,3*S*,4*R*,5*R*)-7-(Benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-allylheptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline. (*E*)-Oxazoline **9a** was treated with allyllithium (prepared from allyltriphenyltin (1.44 g, 3.7 mmol) and phenyllithium (1.5 M, 2.4 mL, 3.7 mmol) according to the procedure described for the reaction of oxazoline **9a** with methallyllithium (vide supra). The usual workup and flash chromatography (ether) gave the allyloxazoline as a yellow oil: R_f 0.42; 0.20 g (37% yield); FT IR ($CHCl_3$) 3067 (m), 3035 (m), 2930 (s), 2886 (m), 1662 (s), 1496 (m), 1410 (m), 1350 (s), 1288 (m), 1240 (m), 1190 (s), 1130 (s), 986 cm^{-1} (m); NMR (270 MHz, $CDCl_3$) 7.38–7.29 (m, 5 H), 5.76–5.74 (m, 1 H), 5.66–5.07 (m, 3 H), 4.55 (s, 2 H), 4.43 (dd, 1 H, J = 4.8, 3.3 Hz), 4.06–3.99 (m, 1 H), 3.75–3.40 (m, 2 H), 3.53 (s, 3 H), 3.17 (dd, 1 H, J = 5.0, 3.3 Hz), 3.04 (d, 1 H, J = 3.6 Hz), 2.79–2.51 (m, 3 H), 2.36–1.87 (m, 4 H).

(+)-(4*S*,5*S*)-4-(Prop-2-enyl)-5-[(2*R*,3*S*)-4-(benzyloxy)-2-hydroxy-3-methoxybutyl]dihydrofuran-2(3*H*)-one (11b). The above oxazoline adduct (0.15 g, 0.26 mmol) in methanol (3 mL) was treated with a 20% sulfuric acid solution (1.5 mL) as reported for lactone **11a** (vide supra). The usual workup and flash chromatography (ether) gave a clear, pale yellow oil: R_f 0.30; 0.06 g (69% yield); NMR (270 MHz, $CDCl_3$) 7.38–7.26 (m, 5 H), 5.76–5.66 (m, 1 H), 5.13–5.07 (m, 2 H), 4.52 (s, 2 H), 4.30 (dd, 1 H, J = 4.8 Hz, 3.3 Hz), 4.06–4.00 (m, 1 H), 3.75–3.37 (m, 2 H), 3.53 (s, 3 H), 3.17 (dd, 1 H, J = 4.6 Hz, 3.3 Hz), 3.04 (d, 1 H, J = 3.6 Hz, concentration dependent), 2.79–1.82 (m, 7 H).

(4*S*,5*S*)-2-[(2*S*,3*S*,4*R*,5*R*)-7-(Benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-butylheptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline. A solution of *n*-butyllithium in hexanes (2.4 M, 0.17 mL, 0.4 mmol) was added to 1 mL of dry tetrahydrofuran under a nitrogen atmosphere and this solution was cooled to −78 °C. A solution of (*E*)-oxazoline **9a** (0.20 g, 0.37 mmol) in 1 mL of dry tetrahydrofuran was added dropwise over 20 min. The resulting red-orange solution was stirred at −78 °C for 2 h. The reaction mixture was poured into a 5% sodium bicarbonate solution. Extraction with ether, drying over magnesium sulfate, filtration, and removal of solvent in vacuo gave a clear, yellow oil.

Flash chromatography (ether) gave, after removal of the solvent, the butyl oxazoline as a white solid: R_f 0.33; 0.17 g (78% yield); mp 103–104 °C; FT IR ($CHCl_3$) 3090 (m), 3069 (m), 3034 (m), 2959 (m), 2931 (s), 2895 (s), 2871 (s), 2863 (s), 1661 (s), 1602 (w), 1496 (m), 1455 (m), 1406 (m), 1351 (s), 1246 (m), 1215 (s), 1194 (s), 1161 (s), 1128 (s), 1095 (s), 1029 (s), 912 cm^{-1} (m); NMR (270 MHz, $CDCl_3$) 7.49–7.25 (m, 15 H), 552 (s, 1 H), 5.29 (d, 1 H, J = 6.6 Hz), 4.54 (dd, 2 H, J = 18.5, 12 Hz, AB pattern), 4.14–4.10 (m, 1 H), 4.00–3.75 (m, 1 H), 3.68–3.37 (m, 3 H), 3.57 (s, 3 H), 3.40 (s, 3 H), 3.26 (br s, 1 H), 2.70–2.48 (m, 4 H), 2.40–2.20 (m, 2 H), 2.00–1.30 (m, 7 H), 1.00–0.91 (t, 3 H, J = 6.6 Hz).

Anal. Calcd for $C_{37}H_{47}NO_6$: C, 73.85; H, 7.87; N, 2.32. Found: C, 73.68; H, 7.89; N, 2.30.

(+)-(4*R*,5*R*)-4-Butyl-5-[(1*S*,2*R*)-4-(benzyloxy)-2-hydroxy-1-methoxybutyl]dihydrofuran-2(3*H*)-one (11c). The above butyl oxazoline (0.11 g, 0.18 mmol) was dissolved in 6 mL of methanol. A 10% sulfuric acid solution (6 mL) was added, and the reaction mixture was stirred at 25 °C for 24 h. The aqueous mixture was saturated with sodium chloride and extracted three times with ether. The combined organic layers were dried over sodium carbonate and magnesium sulfate. Filtration and evaporation of solvent in vacuo gave a yellow oil.

Flash chromatography (ether) gave two fractions. Removal of solvent from the first fraction gave benzaldehyde (R_f 0.80; 0.02 g). The second fraction afforded the butyl lactone **11c** as a clear, pale yellow oil: R_f 0.45; 0.04 g (59% yield); FT IR ($CHCl_3$) 3497 (s), 3091 (m), 3069 (m), 3032 (m), 2962 (s), 2934 (s), 2864 (s), 1773 (s), 1495 (w), 1456 (m), 1418 (w), 1364 (m), 1248 (m), 1216 (m), 1183 (s), 1095 (s), 1027 (m), 1006 (m), 928 (m), 899 (s), 864 cm^{-1} (s); NMR (270 MHz, $CDCl_3$) 7.41–7.29 (m, 5 H), 4.73 (dd, 1 H, J = 7.0, 3.0 Hz), 4.53 (s, 2 H), 4.11–4.02 (m, 1 H), 3.98–3.39 (m, 2 H), 3.47 (s, 3 H), 3.34 (dd, 1 H, J = 4.0, 3.0 Hz), 3.20 (d, 1 H, J = 3.3 Hz, concentration dependent), 2.57–2.36 (m, 3 H), 2.00–1.80 (m, 2 H), 1.70–1.30 (m, 4 H), 1.23 (t, 3 H, J = 7.0 Hz); $[\alpha]^{27}_D$ +13.1° (*c* 0.6, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.84; H, 8.39. Found: C, 67.98; H, 8.44.

(4*S*,5*S*)-2-[(2*R*,3*S*,4*R*,5*S*)-7-(Benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-(2-methylpropyl)heptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline. (*E*)-Oxazoline **9a** (0.20 g, 0.37 mmol) was treated with 2-methylpropyllithium [prepared from the corresponding bromide (0.15 g, 1.11 mmol) and lithium dispersion (2% Na, 30% in oil, 5.2 mg, 2.22 mmol) in ether (4 mL) at −30 °C] in analogy to the procedure employing butyllithium (vide supra). The usual workup and flash chromatography (ether) gave 0.22 g of clear pale yellow oil: NMR ($CDCl_3$, 90 MHz) 7.42–7.28 (m, 5 H), 5.52 (s, 1 H), 5.29 (d, 1 H, J = 6.5 Hz), 4.51 (s, 2 H), 4.14–4.10 (m, 1 H), 4.00–3.80 (m, 1 H), 3.68–3.37 (m, 3 H), 3.50 (s, 3 H), 3.40 (s, 3 H), 3.26 (m, 1 H), 2.70–2.48 (m, 4 H), 2.40–2.20 (m, 2 H), 2.0–0.9 (m, 10 H).

(4*R*,5*S*)-4-(2-Methylpropyl)-5-[(1*S*,2*R*)-4-(benzyloxy)-2-hydroxy-1-methoxybutyl]dihydrofuran-2(3*H*)-one (12d). The aforementioned oxazoline (0.22 g) was dissolved in absolute

methanol (3 mL) and was treated with a 20% sulfuric acid solution (1.5 mL) as previously described for lactone 11. The usual workup and flash chromatography (ether) gave 0.08 g (64% yield) of a clear, colorless liquid: FT IR ($CHCl_3$) 3480 (m), 3088 (w), 3070 (w), 3032 (m), 2970 (s), 2941 (s), 2860 (s), 1771 (s), 1489 (m), 1450 (m), 1366 (m), 1220 (m), 1090 (s), 1030 (m), 930 (m), 895 (s); NMR ($CDCl_3$, 270 MHz) 7.49–7.31 (m, 5 H), 4.69 (dd, 1 H, J = 6.9, 2.8 Hz), 4.50 (s, 2 H), 4.11–4.02 (m, 1 H), 3.98–3.39 (m, 2 H), 3.50 (s, 3 H), 3.28 (dd, J = 4.1, 2.8 Hz), 3.1 (m, 1 H, concentration dependent), 2.57–2.36 (m, 3 H), 2.00–1.80 (m, 2 H), 1.70–1.1 (m, 7 H).

Preparation of Lactone 11a via Oxazoline Acetonide 9b. Ester **10** (0.5 g, 1.4 mmol) was dissolved in methanol (20 mL) and cooled to −78 °C. Ozone was bubbled through the stirred solution until a purple-blue color persisted (reaction time 4 min, flow rate 15 mL/min). Excess dimethyl sulfide (5 mL) was added, and the reaction mixture was warmed gradually to 25 °C. The solution was concentrated in vacuo, the residue was taken up in CH_2Cl_2 (15 mL), and the organic solution was washed twice with water, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a pale yellow oil. Flash chromatography (ethyl acetate–hexanes, 3:1) gave the crude glucose **8b**: clear, colorless oil; 0.40 g (90% yield); R_f 0.47; NMR ($CDCl_3$, 90 MHz) 9.60 (s, 1 H), 7.30 (s, 5 H), 4.50 (s, 2 H), 4.20 (d, 1 H, J = 6 Hz), 3.75–3.30 (m, 4 H), 3.40 (s, 3 H), 2.10–1.80 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H).

Sodium hydride (60% in oil, 0.06 g, 1.4 mmol) was washed twice with hexanes under a nitrogen atmosphere. The last traces of solvent were evaporated under a stream of nitrogen, and then DME (3 mL) was added. A solution of oxazoline phosphonate (10.47 g, 1.4 mmol) in 2 mL of DME was added dropwise with stirring over 10 min. After the mixture was cooled to 0 °C, a solution of the protected glucose **8b** (0.4 g, 1.3 mmol) in 2 mL of DME was added dropwise over 10 min. Stirring was continued for 4 h at 0 °C. The reaction mixture was poured into a 5% aqueous sodium bicarbonate solution, and the mixture was extracted three times with ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give a clear, yellow oil. Flash chromatography (ethyl acetate–hexanes, 3:1) gave two products. (1) Glucose **8b**: 0.06 g (15% yield); R_f 0.50. (2) (*E*)-Oxazoline **9b**: 0.48 g (78% yield); R_f 0.31; NMR ($CDCl_3$, 90 MHz) 7.40–7.20 (m, 10 H), 6.90 (dd, 1 H, J = 16, 6 Hz), 6.30 (dd, 1 H, J = 16, 3 Hz), 5.40 (dd, 1 H, J = 6 Hz), 4.55 (s, 2 H), 4.35–4.10 (m, 1 H), 3.70–3.30 (m, 5 H), 3.55 (s, 3 H), 3.40 (s, 3 H), 3.00 (m, 1 H), 2.20–1.80 (m).

The (*E*)-isopropylideneoxazoline (0.4 g, 0.8 mmol) was treated with methallyllithium (3.3 mmol) as described (vide supra) for the (*E*)-benzylideneoxazoline. Hydrolysis of the adduct provided a 90:10 mixture of lactones **11a** and **12a** as a pale yellow oil in 59% yield from the (*E*)-oxazoline. The spectral data was in accord with lactones **11a** and **12a** prepared from benzylideneoxazoline **9a**.

Conversion of Oxazoline 15 to Valerolactone 16a by Reaction with Allyllithium. Oxazoline **15** (0.6 g, 2.18 mmol) was treated with allyllithium [prepared from allyltriphenyltin (4.25 g, 10.9 mmol) and commercial phenyllithium (1.5 M, 7.2 mL, 10.9 mmol) in 12 mL of ether] according to the procedure described for the reaction of oxazoline **9a** with methyllithium (vide supra). The usual workup gave 0.53 g of crude oxazoline adduct.

This adduct was dissolved in ethanol (35 mL) and stirred under a hydrogen atmosphere (1 atm) for 3 h in the presence of 10% Pd/C (0.08 g). Filtration through Celite followed by removal of solvent in vacuo gave 0.5 g of a propyl oxazoline whose spectral properties agreed with those reported by Meyers.

Subsequent conversion to the propylvalerolactone **16a** followed Meyers' procedure and gave spectral data in accord with those reported.[12]

Conversion of Ester 10 to Butyl Lactone 12c. A suspension of cuprous iodide (98%, 1.05 g, 5.44 mmol) in a mixture of tetrahydrofuran (7.5 mL) and ether (7.5 mL) was cooled to −35 °C under a nitrogen atmosphere. A solution of *n*-butyllithium in hexanes (2.4 M, 4.5 mL, 10.9 mmol) was added dropwise over 15 min. The dark brown suspension was stirred at −35 °C for 20 min. A solution of ester **10** (0.5 g, 1.36 mmol) in tetrahydrofuran (2 mL) was added dropwise over 5 min. The reaction mixture was stirred at −35 °C for 2.5 h, poured into a saturated ammonium chloride solution, and diluted with ether (twofold). Air was bubbled through the solution until the organic layer was clear and colorless. The layers were separated, and the organic layer was dried over potassium carbonate and magnesium sulfate. Filtration and removal of solvent in vacuo gave 0.5 g of a yellow oil: NMR ($CDCl_3$, 90 MHz) 7.40–7.26 (m, 5 H), 4.50 (s, 2 H), 3.8–3.6 (m, 4 H), 3.75 (s, 3 H), 3.50 (s, 3 H), 3.15 (t, 1 H, J = 3 Hz), 2.40–2.30 (m, 2 H), 2.10–1.80 (m, 2 H), 1.40–1.20 (m, 13 H), 0.9 (t, 3 H, J = 4 Hz).

The crude ester was dissolved in tetrahydrofuran (10 mL) and treated with a 10% sulfur acid solution (10 mL) for 18 h. The aqueous layer was saturated with salt and extracted three times with ether. The combined organic layers were dried over sodium carbonate and magnesium sulfate, filtered, and concentrated in vacuo.

Flash chromatography (ether) gave 0.5 g (88% yield) of a clear, pale yellow liquid: FT IR ($CHCl_3$) 3492 (s), 3091 (m), 3072 (m), 3032 (m), 2960 (s), 2936 (s), 2862 (s), 1770 (s), 1496 (w), 1449 (w), 1420 (m), 1360 (m), 1244 (m), 1220 (w), 1181 (s), 1090 (s), 1030 (m), 999 (s), 930 (m), 898 (s), 860 cm^{-1} (s); NMR ($CDCl_3$, 270 MHz) 7.33–7.26 (m, 5 H), 4.53 (s, 2 H), 4.38 (dd, 1 H, J = 6.4, 3.6 Hz), 4.10–4.00 (m, 1 H), 3.80–3.58 (m, 2 H), 3.54 (s, 3 H), 3.17 (t, 1 H, J = 3.6 Hz), 2.61–2.55 (m, 3 H), 2.41–2.35 (m, 1 H, concentration dependent), 2.10–2.01 (m, 1 H), 1.95–1.81 (m, 1 H), 1.70–1.68 (m, 6 H), 0.9 (t, 3 H, J = 4.1 Hz).

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Registry No. 2, 19877-09-9; **3a**, 62853-46-7; **3b**, 77234-40-3; **4** (isomer 1), 78249-06-6; **4** (isomer 2), 78249-07-7; **5**, 78249-08-8; **6** (isomer 1), 78249-09-9; **6** (isomer 2), 78306-79-3; **7**, 78249-10-2; **8a**, 78249-11-3; **8b**, 78249-12-4; **9a**, 78249-13-5; **9b**, 78249-14-6; **10**, 77234-43-6; **11a**, 78249-15-7; **11a** diol, 78249-16-8; **11b**, 78249-17-9; **11c**, 78249-18-0; **11d**, 78249-19-1; **12a**, 78306-80-6; **12b**, 78392-34-4; **12c**, 78306-81-7; **12d**, 78306-82-8; **15**, 61198-39-8; **16a**, 69853-70-9; **16b**, 61198-48-9; **16** (R = allyl), 78249-20-4; (−)-(4*S*,5*S*)-2-(diethylphosphonomethyl)-4-methoxymethyl)-5-phenyl-2-oxazoline, 78249-21-5; (−)-(4*S*,5*S*)-2-methyl-4-(methoxymethyl)-5-phenyl-2-oxazoline, 52075-14-6; (−)-(4*S*,5*S*)-2-[(2*S*,3*S*,4*R*,5*S*)-7-(benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-(2-methylprop-2-enyl)heptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline, 78249-22-6; (+)-(4*S*,5*S*)-2-[(2*S*,3*S*,4*R*,5*R*)-7-(benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-allylheptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline, 78249-23-7; (4*S*,5*S*)-2-[(2*S*,3*S*,4*R*,5*R*)-7-(benzyloxy)-3,5-(benzylidenedioxy)-4-methoxy-2-butylheptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline, 78249-24-8; (4*S*,5*S*)-2-[(2*R*,3*S*,4*R*,5*S*)-7-(benzyloxy)-3,5-(benzylidenedioxy-4-methoxy-2-(2-methylpropyl)heptyl]-4-(methoxymethyl)-5-phenyl-2-oxazoline, 78249-25-9.