therefore, it could not be obtained in a sufficiently pure form for identification from these reactions. This product (A) was subsequently identified by independent synthesis (vide infra). From the NMR spectra it was estimated to be present in 7% and 3% yields from the 5- and 15-min reactions, respectively.

An additional reaction of **4** was conducted as described above except that lithium triethylborodeuteride (LTBD) replaced LTBH. The results were the same except that deuterium was incorporated into compound **5** at C_4 and into compound **7** in the hydroxymethyl group.

Photolysis of 3,6-Dideoxy-2-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranoside (5). Compound **5** was photolyzed in the manner described above for the ditosylate **4**. This reaction converted 414 mg (1.31 mmol) of **4** into 191 mg (1.18 mmol, 90%) of methyl 3,6-dideoxy-α-D-*xylo*-hexopyranoside (**6**), identical in ^1H and ^{13}C NMR spectra with those reported for an independently synthesized sample.[9]

Oxidation of 3,6-Dideoxy-2-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranoside (5). Compound **5** (202 mg, 0.637 mmol) was dissolved in 10 mL of dry methylene chloride. To this stirred solution were added 100 mg (0.12 mmol) of sodium acetate and 540 mg (2.5 mmol) of pyridinium chlorochromate. The reaction mixture became dark after a few minutes. After 2 h, the reaction mixture was passed through a 5 × 10 cm column of silica gel by eluting with 1:1 ethyl ether–methylene chloride. This process removed the colored material. Concentration of the reaction mixture under reduced pressure gave 198 mg (0.62 mmol, 98%) of methyl 3,6-dideoxy-2-*O*-*p*-tolylsulfonyl-α-D-*erythro*-hexopyranosid-4-ulose (**8**), mp 84–85 °C. This material was identified by its ^1H and ^{13}C NMR spectra and by its subsequent reduction to **5**. Compound **8** was relatively unstable. It decomposed in solution in several hours.

Reaction of 3,6-Dideoxy-2-*O*-*p*-tolylsulfonyl-α-D-*erythro*-hexopyranosid-4-ulose (8) with LTBH. Compound **8** (198 mg, 0.62 mmol) was reacted with LTBH according to the procedure used for synthesis of **4** from **3**. After workup, compound **5** crystallized from the reaction mixture. The residue after crystallization was chromatographed on a 5 × 20 cm column of silica gel to give an additional quantity of **5**, bringing the total isolated yield to 126 mg (0.40 mmol, 60%). Also isolated was 64 mg (0.19 mmol, 35%) of a solid identified as methyl 3,6-dideoxy-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranoside (**9**), mp 109–111 °C, on the basis of its NMR spectra and its photochemical deprotection to give methyl 3,6-dideoxy-α-D-*ribo*-hexopyranoside (**10**). Anal. Calcd for $C_{14}H_{20}O_6S$: C, 53.15; H, 6.37. Found: C, 52.87; H, 6.31.

Photolysis of 3,6-Dideoxy-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranoside (9). Compound **9** was photolyzed in the manner described for photolysis of **4**. This reaction converted 64 mg (0.19 mmol) of **9** into 30 mg (0.18 mmol) of methyl 3,6-dideoxy-α-D-*ribo*-hexopyranoside (**10**), identical in ^1H and ^{13}C NMR spectra with those reported for an independently synthesized sample.[10]

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Registry No. **2**, 3396-99-4; **3**, 74052-05-4; **4**, 99310-36-8; **5**, 99310-37-9; **6**, 6109-60-0; **7**, 99310-38-0; **8**, 99310-39-1; **9**, 99310-40-4; **10**, 31899-66-8; LTBH, 22560-16-3; methyl 6-deoxy-α-D-galactopyranoside, 1128-40-1.

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A Chiral Synthesis of (+)-Lineatin, the Aggregation Pheromone of *Trypodendron lineatum* (Olivier), from D-Ribonolactone

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Lineatin, the aggregation pheromone of *Trypodendron lineatum* (Olivier), has been shown to be (+)-(1*R*,4*S*,5*R*,7*R*)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]nonane, (+)-**1**, by the first stereospecific chiral synthesis. D-Ribonolactone (**3**) was used to prepare (2*S*,3*R*)-2,3-(isopropylidenedioxy)-4-methyl-4-[[2-(trimethylsilyl)ethoxy]methoxy]pentanal (**12**). Condensation with the cyanophosphonate **7** provided two isomeric α,β-unsaturated nitriles, **13**. Catalytic hydrogenation furnished (3*RS*,5*R*,6*R*)-3-cyano-5,6-(isopropylidenedioxy)-7-methyl-7-[[2-(trimethylsilyl)ethoxy]methoxy]-1,1-dimethoxyoctane (**14**), which, upon acid-catalyzed hydrolysis, produced the diastereoisomeric mixture **17**. Blocking of the hemiacetal function of **17** with a *tert*-butyldimethylsilyl group, followed by reaction with methanesulfonyl chloride, produced the mixture **22**. Acid-catalyzed cyclization of the deprotected hemiacetal **23** yielded (1*R*,4*R*,5*R*,7*S*)-7-cyano-3,3-dimethyl-4-[(methylsulfonyl)oxy]-2,9-dioxabicyclo[3.3.1]nonane (**24**). Intramolecular nucleophilic ring closure provided (1*R*,4*S*,5*R*,7*S*)-7-cyano-3,3-dimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]nonane (**25**). Conversion of the cyano group to a methyl group using diisobutylaluminum hydride, followed by Wolff–Kishner reduction, produced (+)-**1**. This 16-step synthetic route to (+)-lineatin clearly established the absolute configuration as 1*R*,4*S*,5*R*,7*R* and produced (+)-lineatin in 2.7% overall yield.

Lineatin (**1**), an aggregation pheromone from the frass of the female ambrosia beetle *Trypodendron lineatum* (Olivier),[1] has been shown to elicit powerful secondary attraction in laboratory and field trials.[2,3] The extensive damage to fallen and sawn timber, especially Douglas fir, caused by this beetle lends particular significance to the use of this semiochemical as a possible means for maintaining control of this pest.[4–6] Entomological investigations have demonstrated not only that (+)-**1** is the active

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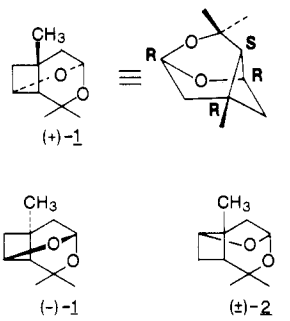
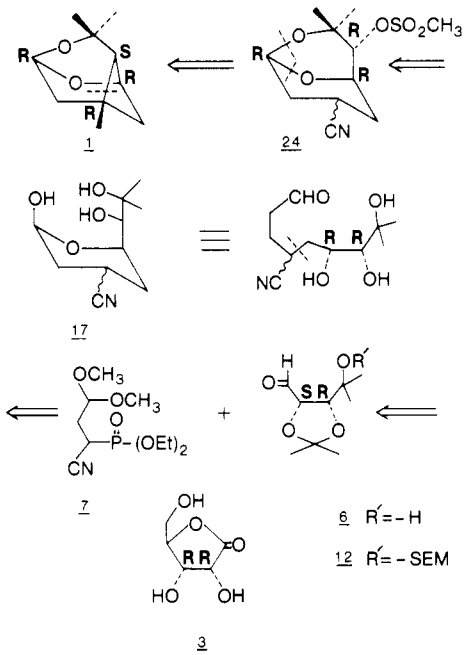


Figure 1. (+)-Lineatin [(+)-1], (−)-lineatin [(−)-1], and isolineatin [(±)-2].

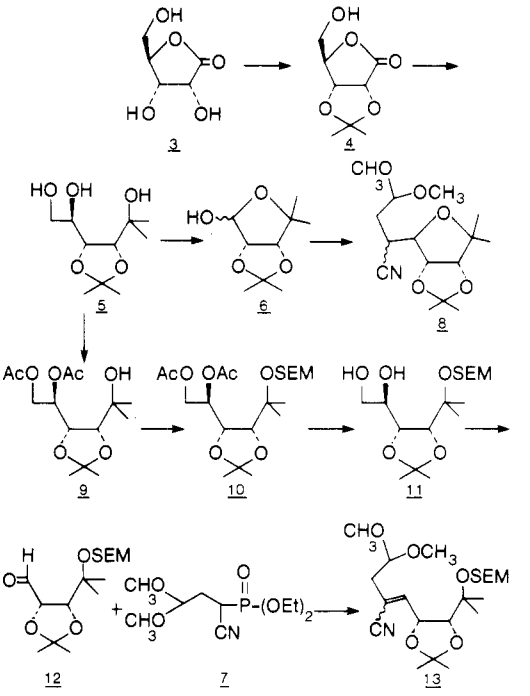
Scheme I. Retrosynthetic Analysis of the Synthetic Approach



enantiomer[5] (Figure 1) but that both its enantiomer, (−)-1, and its regioisomer, (±)-2, were neither attractive nor inhibitory. Consequently, all efforts aimed at large-scale syntheses have been directed toward production of racemic lineatin (±)-1.[7-13] Enantiomers of lineatin (1) have been produced by resolution of diastereoisomeric derivatives of intermediates.[7-9] The disputed absolute stereochemistry of the natural semiochemical,[7,8] as assigned from resolved diastereoisomers, prompted us to prepare the expected enantiomer via an unambiguous chiral route. During the course of this work, an X-ray crystal structure determination[9] of a diastereoisomeric derivative of an intermediate resolved the controversy and established the absolute configuration of (+)-1 to be 1*R*, as shown in Figure 1 and established by this synthetic study.

As indicated in the retrosynthetic analysis (Scheme I), the systematic introduction of functional groups onto commercially available D-ribonolactone provided a chiral

Scheme II. Synthetic Transformations Leading to α,β-Unsaturated Nitriles 13



framework of known absolute configuration. The target tricyclic acetal (+)-1 would be expected from the reduction of the favored 4-*exo*-Tet ring closure[14] product of the dioxabicyclo[3.3.1]nonane cyano mesylate **24**. It was envisaged that acid-catalyzed cyclization of the aldehydo triol **17** would provide the bicyclo[3.3.1]nonane acetal **24**. Condensation of the ylide derived from phosphonate **7** and the chiral aldehyde **6** or **12**, followed by reduction and deprotection, was expected to yield the aldehydo triol **17**. The chiral aldehyde **6** or **12** was readily obtained from D-ribonolactone (**3**).

Discussion

D-(+)-Ribonolactone (**3**) was converted to the known 2,3-*O*-isopropylidene-D-(−)-ribonolactone[15] (**4**), followed by Grignard reaction with excess methylmagnesium iodide to produce the triol **5** (Scheme II). Sodium metaperiodate oxidation[16] of the vicinal diol produced the masked aldehyde **6**. Condensation of **6** and phosphonate **7** under the conditions described by Rosenthal et al.[17] failed to produce the required α,β-unsaturated nitrile. Instead, the starting aldehyde **6** was isolated together with saturated nitrile **8** produced by intramolecular conjugate addition of the α,β-unsaturated nitrile.

To prevent conjugate addition, it was necessary to block the tertiary hydroxyl group with a protecting group removable under very mild conditions. Triol **5** was treated with acetic anhydride and pyridine to produce the crystalline diacetate **9** in 75% yield. The tertiary hydroxyl group was protected by treatment with [β-(trimethylsilyl)ethoxy]methyl chloride[18] in refluxing tetrahydrofuran to produce **10**, and the diol **11** was regenerated using 5% aqueous sodium hydroxide. When **11** was subjected to the action of aqueous sodium metaperiodate,[16] (2*S*,3*R*)-2,3-(isopropylidenedioxy)-4-methyl-4-[[2-(trimethylsilyl)eth-

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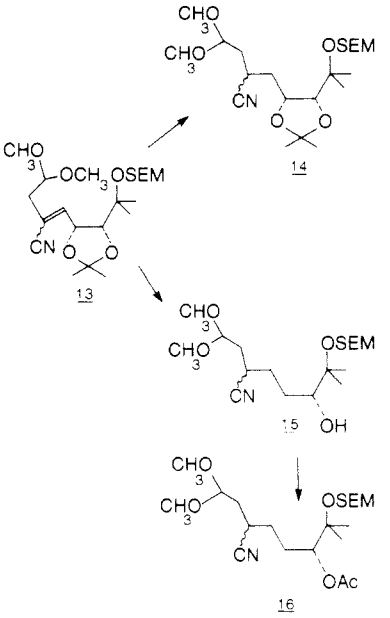
Scheme III. Reduction of Ene Nitrile 13



oxy]methoxy]pentanal (12) was produced in 95% yield.

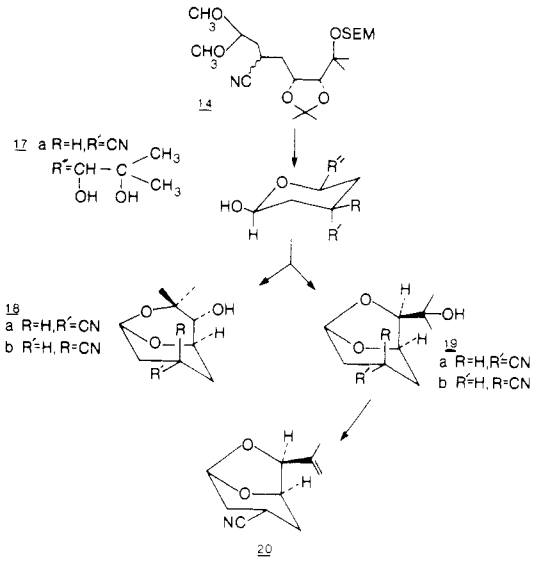
Condensation of 12 and the ylide derived from 7 furnished 13 in 90% yield. ^{1}H NMR revealed the presence of E/Z isomers in a ratio of 4:1, as was evident from the doubleted triplets at 6.45 ppm (J = 1, 10 Hz) corresponding to the olefinic hydrogen of the E isomer. The *cisoid* nature of the 1,3-dioxolane ring appeared to remain intact under the conditions employed in this condensation, as indicated by the magnitude of the ^{1}H NMR coupling constant in the dioxolane ring. As the next step was to convert the α,β-unsaturated nitrile mixture **13** to the saturated nitrile **14**, in which the precursor identity of the double bond would be lost, separation of the geometric isomers was not attempted.

When the ene nitrile **13** was subjected to the action of magnesium and methanol, according to the method described by Profitt et al.[19] a reductive elimination product **15** was produced and identified by conversion to the monoacetate **16**. However, catalytic hydrogenation using 5% palladium on carbon was successful and furnished the desired saturated nitrile **14** in 97% yield (Scheme III).

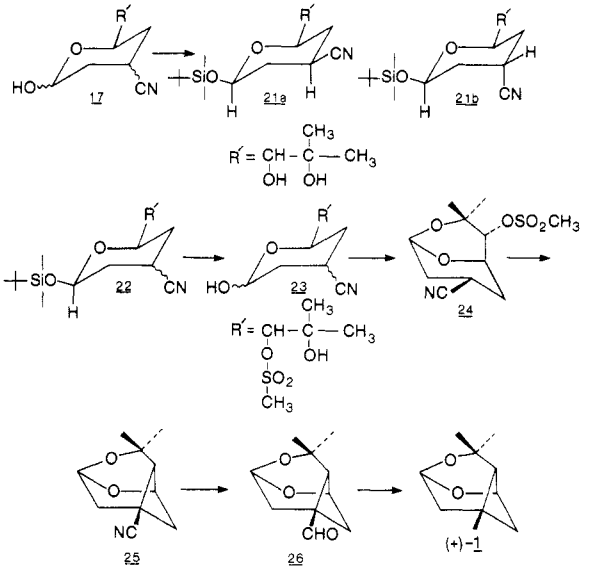
Complete hydrolysis of **14** to precursor **17** was found to proceed smoothly and cleanly with methanol–1% aqueous sulfuric acid (1:1) to produce a mixture of diastereoisomers **17** in 90% yield (Scheme IV). The ratio of these diastereoisomers was found by ^{1}H NMR to be 3:2, in which the more polar diastereoisomer prevailed. Trituration of the mixture with dichloromethane enabled isolation of **17a** from the mixture as colorless crystals. The remainder of the hydrolysis product failed to crystallize, and attempts at further separation were not successful. The assumption that the minor component in the mixture was the other epimeric nitrile with an equatorial orientation was substantiated at a later stage when the (*tert*-butyldimethylsilyl)oxy derivatives **21a** and **21b** were separated by chromatography.

Intramolecular acetal formation of the cyano epimers **17** can produce four cyclized products: two diastereoisomers resulting from cyclization between the anomeric hydroxyl group and tertiary hydroxyl group to produce 2,9-dioxabicyclo[3.3.1]nonane derivatives **18a** and **18b** and two diastereoisomers resulting from cyclization between the anomeric hydroxyl group and secondary hydroxyl

Scheme IV. Acid-Catalyzed Cyclization of Saturated Nitrile 14



Scheme V. Synthetic Transformations Leading to (+)-Lineatin, (+)-1



group to produce 6,8-dioxabicyclo[3.2.1]octane derivatives **19a** and **19b** (Scheme IV). When **17a** in methylene chloride was treated with a catalytic amount of *p*-toluenesulfonic acid, **19a** was produced. The same product was isolated when the epimeric mixture **17** was treated in the same manner. The structure of **19a** was established from ^{1}H NMR coupling constants of the CHCN and a NOE experiment that showed enhancement of the hydroxyl hydrogen upon irradiation of CHCN. Cyclization had preferentially produced the nonproductive bicyclooctane by a disfavored 5-*endo*-Trig[14] ring closure rather than the desired bicyclononane by the favored 6-*endo*-Trig ring closure. When **19a** in chloroform was treated with *p*-toluenesulfonic acid for 14 days at room temperature, **19a** was recovered quantitatively. Treatment of **19a** with methanesulfonyl chloride and triethylamine[20] produced olefin **20** in 32% yield.

To obtain the required 2,9-dioxabicyclo[3.3.1]nonane ring system by intramolecular acetal cyclization, the secondary hydroxyl group in the diastereoisomeric triol was

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blocked in the following manner. The diastereoisomeric mixture **17** was treated with *tert*-butyldimethylsilyl chloride, according to the procedure described by Kraska et al.,[21] to produce **21a** and **21b** as a readily separable mixture of diastereoisomers in 84% yield (Scheme V). Protection of the secondary hydroxyl group was accomplished with a mesylate ester that would later be displaced to form the tricyclic ring system and yet was stable to the acidic conditions required for the cyclization. The mesylate **22** was isolated in 77% yield. Regeneration of the hemiacetal portion was accomplished using 5% aqueous hydrofluoric acid,[22] providing mixture **23**, which was cyclized by refluxing in benzene containing *p*-toluenesulfonic acid using a Dean–Stark trap. A mixture of several components was produced in which **24a**, the major component, was isolated in 33% yield. NOE of C_4-H was observed when CHCN was irradiated as would be expected for the postulated 2,9-dioxabicyclo[3.3.1]nonane ring system.

The stereospecific cyclobutane ring formation was accomplished by using freshly prepared potassium amide in refluxing THF on the cyano mesylate **24a** to produce the tricyclic cyano acetal **25** in 69% yield. Reduction with diisobutylaluminum hydride[23] produced the aldehyde **26** in 75% yield, followed by a Wolff–Kishner reduction using anhydrous hydrazine and potassium hydroxide[24] to produce (+)-lineatin, (+)-**1**, in 73% yield. (+)-Lineatin, (+)-**1**, was produced in 2.7% yield from D-ribonolactone and was uncontaminated by any other volatile material, as judged by capillary gas chromatography. The product exhibited all the spectral properties reported for natural lineatin.[1]

Experimental Section

Evaporation was carried out under reduced pressure at temperatures not exceeding 45 °C. Unless otherwise specified, the following experimental methods were used. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Infrared spectra were run as a neat film on NaCl plates or as solutions in a cell with NaCl windows.

Routine gas liquid chromatography (GC) analyses were run on a Varian 1400 flame ionization gas chromatograph, with glass columns containing supported OV-17 or SE-30, programmed from 80 to 200 °C at 10 °C/min. Thin-layer chromatography (TLC) plates were prepared from silica gel 60G, and compounds were detected by spraying plates with 10% aqueous sulfuric acid and heating. Chromatographic separations were carried out as described by Still et al.[25] using 230–400-mesh silica gel.

Concentrations of optical rotations are reported in grams/100 mL of solvent. Nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ at 400 MHz (J values in Hertz).

Solvents employed for chromatography, petroleum ether (30–60 °C), pentane, and ethyl acetate, were distilled prior to use. Compositions of solvent mixtures are reported as volume ratios. Tetrahydrofuran (THF) was distilled from lithium tetrahydroaluminate. Ether was dried with anhydrous calcium chloride, distilled, and stored over sodium wire. All reactions requiring anhydrous and/or oxygen-free conditions were run under a positive pressure of nitrogen or argon.

2,3-*O*-Isopropylidene-D-ribonolactone (4). To a suspension of D-ribonolactone[26] (**3**; 25 g, 0.17 mol) in acetone (500 mL) was added concentrated sulfuric acid (10 mL) dropwise while the solution was cooled in an ice bath. The mixture was stirred for 5 h at room temperature during which time the starting material dissolved. Ammonia gas was passed through the ice-cooled solution and filtered, and the filtrate was evaporated under reduced pressure. The resulting crystalline residue was recrystallized from benzene to yield the product **4** (28.2 g, 85%) as colorless needles: mp 138–139 °C, $[\alpha]^{23}_D$ −83.2° (*c* 2.48, acetone); lit.[15] mp 138–139 °C, $[\alpha]^{23}_D$ −84.2° (*c* 0.9, acetone).

(2*R*,3*R*,4*R*)-3,4-(Isopropylidenedioxy)-5-methyl-1,2,5-hexanetriol (5). To a solution of methylmagnesium iodide prepared from magnesium (4.85 g, 202 mmol) and methyl iodide (28.68 g, 202 mmol) in ether (200 mL) was added 2,3-*O*-isopropylidene-D-ribonolactone (**4**, 9.4 g, 50 mmol) in dry THF (100 mL) dropwise at room temperature with stirring under argon atmosphere over a period of 0.5 h. The reaction mixture was stirred a further 0.5 h and then refluxed for 5 h. The cooled reaction mixture was treated with saturated ammonium chloride solution (100 mL) and the aqueous layer separated and evaporated to dryness under reduced pressure. The solid was extracted with boiling ethyl acetate (4 × 100 mL), and the combined washings were dried over anhydrous sodium sulfate and evaporated to yield a yellow syrup that was chromatographed with ethyl acetate–ether (1:1) (R_f 0.51) to yield 8.2 g (75%) of **5**: $[\alpha]^{24}_D$ +2.72° (*c* 3.5, MeOH); IR (film) 3320, 2990, 2940, 1375, 1240, 1165, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.82 (1 H, OH, br s), 4.01 (1 H, H_3, dd, $J_{3,4}$ = 5, $J_{2,3}$ = 10), 3.94 (1 H, H4, d, $J_{3,4}$ = 5), 3.91 (2 H, H2, H1, m), 3.65 (1 H, H1, dd, J = 6, 10), 3.59 (1 H, OH, br s), 2.88 (1 H, OH, br s), 1.44 (3 H, CH_3, s), 1.39 (6 H, 2 CH_3, s), 1.31 (3 H, CH_3, s). Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.53; H, 9.27.

(2*RS*,3*S*,4*R*)-5,5-Dimethyl-2-hydroxy-3,4-(isopropylidenedioxy)tetrahydrofuran (6). To a stirred solution of the triol **5** (380 mg, 1.72 mmol) in water (2.5 mL) at 5 °C was added sodium metaperiodate (410 mg, 1.87 mmol) in water (2.5 mL), and the solution was stirred for 2 h. The reaction mixture was extracted with dichloromethane (50 mL), washed with brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was chromatographed with ether–petroleum ether (1:1) to give **6** (290 mg, 90%): $[\alpha]^{24}_D$ +45.8° (*c* 5.33, $CHCl_3$); IR (film) 3310, 2990, 2945, 1465, 1385, 1375, 1255, 1215, 1165, 1015, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (1 H, H_2, dd, $J_{2,3}$ = 4, $J_{2,OH}$ = 12), 4.63 (1 H, H_3, dd, $J_{2,3}$ = 4, $J_{3,4}$ = 6), 4.36 (1 H, H_4, d, $J_{3,4}$ = 6), 3.82 (1 H, OH, d, $J_{2,OH}$ = 12), 1.38 (6 H, $(CH_3)_2$, s), 1.34 (6 H, $(CH_3)_2$, s). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.70; H, 8.69.

Diethyl (3-Cyano-1,1-dimethoxypropyl)phosphonate (7). To a solution of lithium diisopropylamide (845 mmol from equimolar amounts of *n*-butyllithium and diisopropylamine at 0 in anhydrous THF (800 mL), cooled to −78 °C under argon, was added β-cyanopropionaldehyde dimethyl acetal[27] (53.8 g, 417 mmol) in anhydrous THF dropwise over a period of 1 h. The mixture was stirred for 1.5 h, a solution of diethyl chlorophosphate (71.96 g, 417 mmol) in THF (100 mL) was added dropwise over a period of 0.5 h, and stirring was continued for an additional 3 h. The solution was warmed to −40 °C and stirred for an additional 2 h. The reaction mixture was poured into water (600 mL), and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with brine (2 × 200 mL), dried over anhydrous sodium sulfate, and concentrated to give a pale orange oil. This product was subjected to column chromatography using ether to afford 98.2 g (89.0%) of a pale orange oil, **7**: IR (film) 2978, 2830, 2238, 1440, 1385, 1365, 1255, 1030, 960, 830, 790, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.57 (1 H, OCHO, dd, J = 4, 7), 4.22 (4 H, 2 OCH_2CH_3, m), 3.38 (6 H, $(CH_3O)_2$, s), 3.08 (1 H, CHCN, ddd, J = 4, 11, 23), 2.01 (2 H, CH_2CH, m), 1.38 (6 H, $(CH_3)_2$, t, J = 7). Anal. Calcd for $C_{10}H_{20}NO_5P$: C, 45.28; H, 7.54; N, 5.28. Found: C, 44.90; H, 7.90; N, 5.18.

Condensation of 6 and 7. Diethyl (3-cyano-1,1-dimethoxypropyl)phosphonate (**7**; 3.08 g, 1.16 mmol) and sodium hydride (0.50 g of 50% dispersion in mineral oil) were stirred together in anhydrous THF (20 mL) under argon at room temperature until hydrogen evolution had subsided (10 min). A solution of aldehyde **6** (1 g, 5.3 mmol) in THF (10 mL) was added, and stirring continued for 3 h. Water (30 mL) was added to the reaction mixture.

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The aqueous suspension was extracted with dichloromethane (3 × 20 mL), and the extract was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oil (3.82 g) that was subjected to column chromatography with ether–petroleum ether (1:1) to give an inseparable mixture (0.9 g) of unreacted aldehyde **6** and a Michael-type product in a ratio of ≃10:1.7, as indicated by capillary GC.

(2*R*,3*R*,4*R*)-1,2-Diacetoxy-3,4-(isopropylidenedioxy)-5-methylhexan-5-ol (9). Triol **5** (10.0 g, 45.3 mmol) was acetylated with acetic anhydride (50 mL) in pyridine (50 mL) at room temperature for 12 h. The solution was poured into ice-cold water (100 mL), extracted with dichloromethane (2 × 100 mL), washed with ice-cold 1 M hydrochloric acid (2 × 25 mL) and water (2 × 50 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded solid **9** (10.2 g, 75%). Recrystallization from petroleum ether (60–80 °C) and dichloromethane (5:2) gave **9** as colorless crystals: mp 125–126 °C; $[\alpha]^{24}_D$ +51.3° (*c* 7.33, MeOH); IR (KBr) 3472, 2970, 2940, 2865, 1735, 1380, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.29 (1 H, H_2, m), 4.59 (1 H, H_1, dd, $J_{1,2}$ = 3, J = 11), 4.29 (1 H, H_3, dd, $J_{3,4}$ = 5, $J_{2,3}$ = 6), 4.15 (1 H, $H_{1'}$, dd, $J_{1',2}$ = 5, $J_{1,1'}$ = 11), 3.92 (1 H, H_4, d, $J_{3,4}$ = 5), 2.05 (6 H, 2 CH_3CO, s), 1.86 (1 H, OH, br s), 1.50 (3 H, CH_3, s), 1.35 (9 H, 3 CH_3, s). Anal. Calcd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 55.35; H, 8.15.

(2*R*,3*R*,4*R*)-1,2-Diacetoxy-3,4-(isopropylidenedioxy)-5-methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]hexane (10). The diacetate **9** (12.16 g, 40 mmol) was refluxed with diisopropylethylamine (25.8 g, 200 mmol) and [β-(trimethylsilyl)ethoxy]methyl chloride (19.9 g, 120 mmol) in THF (40 mL) under argon atmosphere for 3 h. The mixture was poured into ice water (200 mL), extracted with dichloromethane (2 × 100 mL), washed with brine (100 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave a yellow syrup, which was chromatographed with ether–petroleum ether (1:1) (R_f 0.75) to give the silyl ether **10** (15.20 g, 88%): $[\alpha]^{24}_D$ +9.9° (*c* 18.4, $CHCl_3$); IR (film) 3120, 2980, 2920, 1755, 1385, 1255, 1235, 870, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.35 (1 H, H_2, m), 4.87 (1 H, OCH_2O, d, J = 6), 4.67 (1 H, OCH_2O, d, J = 6), 4.55 (1 H, $H_{1'}$, dd, $J_{1',2}$ = 2, $J_{1,1'}$ = 11), 4.28 (1 H, H_3, t, J = 5), 4.21 (1 H, H_1, dd, $J_{1,2}$ = 5, $J_{1,1'}$ = 11), 3.90 (1 H, H_4, d, $J_{3,4}$ = 5), 3.58 (2 H, OCH_2CH_2, m), 2.05 (6 H, 2 CH_3CO, s), 1.48 (3 H, CH_3, s), 1.42 (3 H, CH_3, s), 1.36 (3 H, CH_3, s), 1.33 (3 H, CH_3, s), 0.91 (2 H, CH_2Si, t, J = 8.4), 0.00 (9 H, $Si(CH_3)_3$, s). Anal. Calcd for $C_{20}H_{38}O_8Si$: C, 55.29; H, 8.75. Found: C, 55.50; H, 9.01.

(2*R*,3*R*,4*R*)-3,4-(Isopropylidenedioxy)-5-methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1,2-hexanediol (11). The diacetate silyl ether **10** (15.21 g, 35.1 mmol) was stirred with 10% sodium hydroxide in methanol–water (1:1, 150 mL) at room temperature for 12 h. The resulting solution was evaporated, dissolved in water (100 mL), and extracted with dichloromethane (3 × 75 mL). The combined extract was washed with brine (100 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a syrup. Chromatography with ether yielded **11** (12.3 g, 100%): $[\alpha]^{24}_D$ −2.1° (*c* 4.02, $CHCl_3$); IR (film) 3450, 2992, 2960, 1385, 1372, 1252, 1218, 1160, 1102, 925, 868, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.96 (1 H, OCH_2O, d, J = 7), 4.82 (1 H, OCH_2O, d, J = 7), 4.68 (1 H, OH, d, J = 2.5), 4.08 (1 H, H_3, dd, $J_{3,4}$ = 5.5, $J_{2,3}$ = 9.8), 4.02 (1 H, H_2, ddd, $J_{2,OH}$ = 2.5, $J_{1,2}$ = 5, $J_{2,3}$ = 9.8), 3.95 (1 H, H_4, d, $J_{3,4}$ = 5.5), 3.85 (1 H, $H_{1'}$, m), 3.69–3.56 (3 H, H_1, OCH_2CH_2, m), 2.27 (1 H, OH, t, J = 6), 1.48 (3 H, CH_3, s), 1.45 (3 H, CH_3, s), 1.41 (3 H, CH_3, s), 1.34 (3 H, CH_3, s), 0.94 (2 H, CH_2Si, t, J = 8.4), 0.00 (9 H, $(CH_3)_3Si$, s). Anal. Calcd for $C_{16}H_{34}O_6Si$: C, 54.71; H, 9.71. Found: C, 54.29; H, 10.05.

(2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-methyl-4-[[2-(trimethylsilyl)ethoxy]methoxy]pentanal (12). A solution of the diol **11** (11.8 g, 33.7 mmol) in water (80 mL) was stirred at 0 °C, a solution of sodium metaperiodate (7.21 g, 33.7 mmol) in water (80 mL) was added over a period of 15 min, and stirring was continued for a further 3 h. The reaction mixture was extracted with dichloromethane (2 × 100 mL), washed with brine (100 mL), and dried over anhydrous sodium sulfate. Evaporation of the dichloromethane and chromatography with ether–petroleum ether (1:2) gave the aldehyde **12** (10.0 g, 95%) (R_f 0.85): $[\alpha]^{24}_D$ +9.4° (*c* 16.4, $CHCl_3$); IR (film) 2975, 2870, 2695, 1728, 1462, 1395, 1385, 1250, 1218, 1065, 915, 862, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.54 (1 H, CHO, d, J = 2), 4.83 (1 H, OCH_2O, d, J = 6), 4.67 (1 H, OCH_2O, d, J = 6), 4.39 (1 H, H_2, dd, $J_{1,2}$ = 2, $J_{2,3}$ = 6), 4.23 (1 H, H_3, d, $J_{2,3}$ = 6), 3.58 (2 H, CH_2CH_2Si, m), 1.59 (3 H, CH_3, s), 1.41 (3 H, CH_3, s), 1.37 (3 H, CH_3, s), 1.30 (3 H, CH_3, s), 0.91 (2 H, CH_2Si, t, J = 8), 0.00 (9 H, $(CH_3)_3Si$, s). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.60; H, 9.43. Found: C, 56.78; H, 9.77.

(*E*,*Z*)-(5*R*,6*R*)-3-Cyano-5,6-(isopropylidenedioxy)-7-methyl-7-[[2-(trimethylsilyl)ethoxy]methoxy]-1,1-dimethoxyoct-3-ene (13). A suspension of 50% sodium hydride (7.0 g, 146 mmol) was washed with anhydrous hexane (2 × 10 mL), suspended in anhydrous THF (500 mL), and cooled to 0 °C under argon atmosphere. The phosphonate **7** (38.75 g, 146 mmol) in THF (200 mL) was added over a period of 1 h. After the evolution of hydrogen gas had subsided, the mixture was stirred for an additional 0.5 h. To this cold mixture (≃5 °C) was added a solution of aldehyde **12** (42.6 g, 133 mmol) in THF (200 mL) over a period of 1 h, and the mixture was stirred for an additional 4 h. The reaction was poured into ice water (200 mL) and extracted with dichloromethane (4 × 100 mL); the combined dichloromethane extractions were washed with brine (2 × 100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil that was chromatographed with ether–petroleum ether (1:2) to afford a mixture of *E*/*Z* isomers **13** (51.7 g, 90%): $[\alpha]^{24}_D$ −8.0° (*c* 7.85, $CHCl_3$); IR (film) 3020, 2900, 2220, 1645, 1455, 1380, 1250, 1125, 1065, 1035, 862, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.45 (1 H, H_4, td, $J_{2,4}$ = 1, $J_{4,5}$ = 10), 5.00 (1 H, H_5, dd, $J_{5,6}$ = 6, $J_{4,5}$ = 10), 4.85 (1 H, OCH_2O, d, J = 7), 4.77 (1 H, OCH_2O, d, J = 7), 4.58 (1 H, OCHO, t, J = 5), 4.15 (1 H, H_6, d, $J_{5,6}$ = 6), 3.61 (2 H, OCH_2CH_2, m), 3.36 (6 H, 2 CH_3O, s), 2.55 (2 H, $CH_2C{=}C$, dd, $J_{2,4}$ = 1, $J_{1,2}$ = 5), 1.40 (3 H, CH_3, s), 1.39 (3 H, CH_3, s), 1.35 (3 H, CH_3, s), 1.28 (3 H, CH_3, s), 0.91 (2 H, CH_2Si, t, J = 8), 0.00 (9 H, $(CH_3)_3$, s). Anal. Calcd for $C_{21}H_{39}NO_6Si$: C, 58.74; H, 9.09; N, 3.26. Found: C, 58.53; H, 9.44; N, 3.44.

(3*RS*,6*R*)-6-Acetoxy-3-cyano-7-methyl-7-[[2-(trimethylsilyl)ethoxy]methoxy]-1,1-dimethoxyoctane (16). To the α,β-unsaturated nitrile **13** (6.52, 15.15 mmol) in methanol (151.5 mL) were added magnesium turnings (14.68 g, 0.6 mol, 40 equiv). The exothermic reaction that ensued after 10 min was moderated with an ice bath. The reaction was stirred for 1 h at 0 °C and 5 h at 25 °C. To the reaction at 0 °C was added saturated aqueous ammonium chloride solution (300 mL) to afford a clear solution that was extracted with dichloromethane (3 × 150 mL). The dichloromethane solutions were combined, washed with brine (200 mL), dried over anhydrous sodium sulfate, and evaporated to yield an oil. The oil was column chromatographed with ether–petroleum ether (1:1) to furnish **15** (4.2 g, 74.0%), which showed IR absorption bands at 3400 cm^{-1} (OH) and 2235 cm^{-1} (CN). The oil **15** (500 mg, 1.3 mmol) was acetylated in pyridine (5 mL) with acetic anhydride (5 mL) at room temperature for 12 h to afford the cyano acetate **16** (420 mg, 75%) after column chromatography with ether–petroleum ether (1:1): $[\alpha]^{22}_D$ −4.0° (*c* 7.9, $CHCl_3$); IR (film) 2950, 2900, 2838, 2250, 1740, 1375, 1248, 1060, 1030, 865, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.85 (1 H, H_6, dd, J = 2.6, J = 10.1), 4.79 (1 H, OCH_2O, d, J = 7.6), 4.72 (1 H, OCH_2O, d, J = 7.6), 4.54 (1 H, OCHO, dd, J = 4.3, J = 7.3), 3.65–3.54 (2 H, OCH_2CH_2, m), 3.38 (3 H, CH_3O, s), 3.50 (3 H, CH_3O, s), 2.82–2.65 (1 H, CHCN, m), 2.14 (3 H, CH_3CO, s), 1.98–1.55 (6 H, $(CH_2)_3$, m), 1.22 (6 H, $(CH_3)_2$, s), 0.91 (2 H, $CH_2Si(CH_3)_3$, t, J = 8.2), 0.07 (9 H, $(CH_3)_3Si$, s). Anal. Calcd for $C_{20}H_{39}NO_6Si$: C, 57.52; H, 9.41; N, 3.35. Found: C, 57.41; H, 9.64; N, 3.55.

(3*RS*,5*R*,6*R*)-3-Cyano-5,6-(isopropylidenedioxy)-7-methyl-7-[[2-(trimethylsilyl)ethoxy]methoxy]-1,1-dimethoxyoctane (14). A solution of the unsaturated nitrile **13** (40.0 g, 72.2 mmol) in 100% ethanol (400 mL) containing 5% palladium on charcoal (4.0 g) was stirred under hydrogen at 1 atm and room temperature for 12 h. The mixture was filtered, evaproated, and chromatographed with ether–petroleum ether (1:1) as eluant to give an oil (39.2 g, 97%). The saturated nitrile **14** exhibited a double spot on TLC with R_f 0.78 and 0.80 corresponding to the two diastereoisomers: $[\alpha]^{24}_D$ +14.0° (*c* 11.4, $CHCl_3$); IR (film) 2992, 2960, 2907, 2840, 2242, 1462, 1439, 1382, 1375, 1255, 1220, 1168, 1061, 940, 925 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.84 (1 H, OCH_2O, d, J = 7.4), 4.73 (1 H, OCH_2O, d, J = 7.4), 4.60 (1 H, OCHO, dd, J = 4.5, J = 7.3), 4.23 (1 H, H_5, ddd, $J_{4,5}$ = 5, $J_{5,6}$ = 6, $J_{4,5}$ = 9), 3.88 (1 H, H6, d, $J_{5,6}$ = 6), 3.69–3.58 (2 H, OCH_2, m), 3.37 (3 H, CH_3O, s), 3.36 (3 H, CH_3O, s), 2.92–2.15 (1 H, CHCN, m), 2.15–1.85 (4 H, 2 H_2, 2 H_4, m), 1.33 (9 H, 3 CH_3, s), 1.28 (3 H, CH_3, s), 0.91

(2 H, CH_2Si, t, J = 8.5), 0.00 (9 H, $(CH_3)_3Si$, s). Anal. Calcd for $C_{21}H_{41}NO_6Si$: C, 58.46; H, 9.51; N, 3.24. Found: C, 58.11; H, 9.80; N, 3.38.

(1′*R*,2*S*,4*S*,6*R*)-4-Cyano-2-hydroxy-6-(1′,2′-dihydroxy-2′-methylpropyl)tetrahydropyran (17a). A solution of the nitrile **14** (21.0 g, 48.7 mmol) in methanol (210 mL) and 1% aqueous sulfuric acid (210 mL) was stirred at room temperature. The hydrolysis was monitored by TLC (ethyl acetate) that indicated after 36–48 h the appearance of two slow-running components (R_f 0.33, R_f 0.25) and disappearance of **14**. After hydrolysis, the solution was cooled to 0 °C and neutralized with 6 M ammonium hydroxide (13 mL). The solution was evaporated to yield a syrup that was subjected to column chromatography using ethyl acetate to furnish 9.3 g (90%) of a colorless syrup. The syrup was diluted with dichloromethane whereupon a solid **17a** was crystallized out (3.8 g) (R_f 0.25): mp 144–147 °C from ethyl acetate; $[\alpha]^{24}_D$ −0.5° (*c* 1.99, MeOH). The remaining solution failed to crystallize further and was used for the next reaction as a mixture of diastereoisomers. The slower eluting nitrile (major) **17a** exhibited the following spectral characteristics: IR (Nujol) 3400, 2950, 2910, 2845, 2230, 1450, 1201, 1190, 1170, 1038, 1005, 955, 907, 885, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.15 (1 H, H_2, ddd, $J_{2,3eq}$ = 2, $J_{2,OH}$ = 6, $J_{2,3ax}$ = 10), 3.99 (1 H, H_6, ddd, $J_{5eq,6}$ = 2, $J_{5ax,6}$ = 11, $J_{1',6}$ = 6), 3.55 (1 H, $H_{1'}$, dd, $J_{1',OH}$ = 4, $J_{1',6}$ = 6), 3.23 (1 H, CHCN, septet, J = 2.5, 5), 3.19 (1 H, OH, d, J = 6), 2.81 (1 H, OH, br s), 2.50–1.61 (5 H, H_{3eq}, H_{3ax}, H_{5ax}, H_{5eq}, OH, m), 1.33 (3 H, CH_3, s), 1.25 (3 H, CH_3, s). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.45; H, 8.19; N, 6.70.

(1*R*,3*S*,5*R*,7*R*)-3-Cyano-7-(2-hydroxypropyl)-6,8-dioxabicyclo[3.2.1]octane (19a). A suspension of **17a** (200 mg, 0.92 mmol) in dichloromethane (10 mL) containing *p*-toluenesulfonic acid (1 mg) was stirred at room temperature for 4 h. The solution was diluted with dichloromethane (20 mL), washed with cold 5% sodium bicarbonate (5 mL) and brine (20 mL), and dried over anhydrous sodium sulfate. Column chromatography using ether–petroleum ether (2:1) afforded the bicyclic alcohol **19a** (120 mg, 65%) (R_f 0.40): $[\alpha]^{24}_D$ +78.4° (*c* 12.42, $CHCl_3$); IR (film) 3490, 2980, 2948, 2890, 2252, 1472, 1447, 1385, 1362, 1300, 1268, 1248, 1230, 1183, 1168, 1125, 1075, 1038, 1015, 996, 980, 960, 917, 895, 882, 835, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.58 (1 H, H_5, br s), 4.27 (1 H, H1, t, $J_{1,7}$ = 3.5), 3.95 (1 H, CHCN, tt, J = 6.5, 12), 3.68 (1 H, H_7, d, $J_{1,7}$ = 3.5), 2.32 (1 H, H_{2eq}, dd, $J_{2eq,3}$ = 6.5, $J_{2eq,2ax}$ = 13), 2.13 (2 H, H_{4eq}, H_{2ax}, m), 1.98 (1 H, H_{4ax}, dt, $J_{4ax,5}$ = 1, $J_{4ax,4eq}$ = 12), 1.79 (1 H, OH, br s), 1.42 (3 H, CH_3, s), 1.23 (3 H, CH_3, s). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.71; H, 7.98; N, 7.18.

(1*R*,3*S*,5*R*,7*R*)-3-Cyano-7-isopropenyl-6,8-dioxabicyclo[3.2.1]octane (20). To a solution of the hydroxy nitrile **19a** (120 mg, 0.61 mmol) and triethylamine (250 mg, 2.52 mol) in dichloromethane (3 mL) at 0 °C under argon was added methanesulfonyl chloride (140 mg, 1.23 mmol) dropwise. After 15 min the ice bath was removed and the reaction stirred for 2 h at room temperature. The reaction mixture was transferred to a separatory funnel with the aid of more dichloromethane (50 mL) and was extracted first with ice water (50 mL), followed by cold 10% aqueous hydrochloric acid (20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and brine (2 × 30 mL). Column chromatography of the crude product using ether–petroleum ether (1:1) yielded the olefin **20** (35 mg, 32%, R_f 0.63) and unreacted alcohol **19a** (50 mg): $[\alpha]^{24}_D$ +78.2° (*c* 2.08, $CHCl_3$); IR (film) 3090, 2970, 2938, 2860, 2245, 1658, 1445, 1355, 1335, 1158, 1125, 1108, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.64 (1 H, H_5, br s), 5.33 (1 H, H7, dt, J = 1, 3), 5.16 (1 H, C=CH, dd, J = 1.5, 5), 4.42 (2 H, C=CH, H_1, m), 3.44 (1 H, CHCN, tt, $J_{2eq,3}$ = $J_{3,4eq}$ = 6, $J_{2ax,3}$ = $J_{3,4ax}$ = 12), 2.13 (1 H, H_{4eq}, ddd, $J_{4eq,5}$ = 1, $J_{3,4eq}$ = 6, $J_{4eq,4ax}$ = 13), 2.07 (1 H, H_{2ax}, m), 1.98 (1 H, H_{4ax}, ddd, $J_{4ax,5}$ = 1.5, $J_{3,4ax}$ = 12, $J_{4ax,4eq}$ = 13), 1.92 (1 H, H_{2eq}, ddd, $J_{2eq,3}$ = 1.0, $J_{2eq,4eq}$ = 2.5, $J_{1,2eq}$ = 6, $J_{2eq,2ax}$ = 14), 1.75 (3 H, CH_3, dt, J = 1, 2.5). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 67.49; H, 7.62.

(1′*R*,2*R*,4*R*,6*R*)-4-Cyano-2-[(*tert*-butyldimethylsilyl)oxy]-6-(1′,2′-dihydroxy-2′-methylpropyl)tetrahydropyran (21a) and (1′*R*,2*R*,4*S*,6*R*)-4-Cyano-2-[(*tert*-butyldimethylsilyl)oxy]-6-(1′,2′-dihydroxy-2′-methylpropyl)tetrahydropyran (21b). A mixture of the two diastereoisomers **17** (4.0 g, 18.6 mmol) was stirred with imidazole (3.16 g, 46.4 mmol) and *tert*-butyldimethylsilyl chloride (3.37 g, 22.3 mmol) in *N*,*N*-dimethylformamide (10 mL) at 25 °C for 24 h. The major components appeared on TLC with ether–petroleum ether (1:1) as two spots with R_f values of 0.48 and 0.38, as well as several minor fast-running products. The mixture was poured into ice water (50 mL), extracted with dichloromethane (3 × 50 mL), washed with brine (100 mL), and dried over anhydrous sodium sulfate. The two major components were separated by column chromatography using ether–petroleum ether (1:1). The faster eluting nitrile yielded **21a** (2.0 g, R_f 0.48) and the slower eluting nitrile yielded **21b** (3.1 g, R_f 0.38) on solvent evaporation to give a total of 5.1 g (84%).

Nitrile **21a** exhibited the following characteristics: $[\alpha]^{22}_D$ +12.7° (*c* 4.7, $CHCl_3$); IR (film) 3460, 2960, 2935, 2860, 2245, 1465, 1390, 1255, 1165, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.72 (1 H, H_2, dd, J = 2.1, 9.4), 3.52 (1 H, H_6, ddd, $J_{5eq,6}$ = 1.9, $J_{1',6}$ = 6, $J_{5ax,6}$ = 11), 3.47 (1 H, $H_{1'}$, dd, $J_{1',OH}$ = 4, $J_{1',6}$ = 6), 2.75 (1 H, CHCN, dt, $J_{4,5eq}$ = $J_{4,3eq}$ = 4, $J_{4,5ax}$ = $J_{3ax,4}$ = 12), 2.60 (1 H, OH, br s), 2.42 (1 H, OH, d, $J_{1',OH}$ = 4), 2.35–2.07 (2 H, H_{5eq}, H_{3eq}, m), 1.78–1.62 (2 H, H_{5ax}, H_{3ax}, m), 1.29 (3 H, CH_3, s), 1.22 (3 H, CH_3, s), 0.88 (9 H, $(CH_3)_3C$, s), 0.11 (6 H, $(CH_3)_2Si$, s). Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.36; H, 9.42; N, 4.25. Found: C, 58.61; H, 9.42; N, 4.25.

Nitrile **21b** exhibited the following characteristics: $[\alpha]^{24}_D$ +30.8° (*c* 2.25, $CHCl_3$); IR (film) 3420, 2950, 2840, 2230, 1455, 1435, 1378, 1362, 1305, 1245, 1160, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.11 (1 H, H_2, dd, $J_{2,3eq}$ = 2.1, $J_{2,3ax}$ = 9.4), 3.94 (1 H, H_6, ddd, $J_{5eq,6}$ = 1.9, $J_{1',6}$ = 5.4, $J_{5ax,6}$ = 11.4), 3.48 (1 H, $H_{1'}$, br d, $J_{1',6}$ = 5.4), 3.18 (1 H, CHCN, tt, $J_{4eq,5ax}$ = $J_{3ax,4eq}$ = 2.4, $J_{3eq,4eq}$ = $J_{4eq,5eq}$ = 5), 2.55 (1 H, OH, br s), 2.35 (1 H, OH, br s), 2.18 (1 H, H_{5eq}, ddd, $J_{5eq,6}$ = 1.9, $J_{4eq,5eq}$ = 5, $J_{5eq,5ax}$ = 14), 2.01 (1 H, H_{3eq}, ddd, $J_{2,3eq}$ = 2.1, $J_{3eq,4eq}$ = 5, $J_{3eq,3ax}$ = 13.5), 1.73–1.61 (2 H, H_{3ax}, H_{5ax}, m), 1.31 (3 H, CH_3, s), 1.23 (3 H, CH_3, s), 0.89 (9 H, $(CH_3)_3C$, s), 0.13 (6 H, $(CH_3)_2Si$, s). Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.36; H, 9.42; N, 4.25. Found: C, 58.21; H, 9.80; N, 4.39.

(1′*R*,2*R*,4*RS*,6*R*)-4-Cyano-2-[(*tert*-butyldimethylsilyl)oxy]-6-[1′-[(methylsulfonyl)oxy]-2′-hydroxy-2′-methylpropyl]tetrahydropyran (22). To a solution of the silyl ether **21a** and **21b** (1.0 g, 3.03 mmol) in anhydrous pyridine (5 mL) at 0 °C under argon was added distilled methanesulfonyl chloride (0.52 g, 4.55 mmol) over a period of 10 min, and the reaction mixture was stirred at 0 °C for 4 h, followed by further stirring at room temperature for 24 h. Ice (10 g) was added, and the mixture was stirred for 10 min after which the mixture was diluted with dichloromethane (50 mL), washed successively with saturated aqueous copper sulfate solution (3 × 25 mL), water (2 × 10 mL), and brine (2 × 25 mL), and dried with anhydrous sodium sulfate. The solvent was evaporated to give an oil that was chromatographed with ether. A fraction was collected (R_f 0.47–0.49) to yield a mixture of silyl monomesylates **22** (0.95 g, 75%): $[\alpha]^{24}_D$ +39.5° (*c* 2.29, $CHCl_3$); IR (film) 3520, 2960, 2958, 2860, 2240, 1475, 1465, 1448, 1360, 1350, 1258, 1175, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (3 H, CH_3SO_2, s), 1.39 (3 H, CH_3, s), 1.33 (3 H, CH_3, s), 0.89 (9 H, $(CH_3)_3C$, s).

(1′*R*,2*RS*,4*RS*,6*R*)-4-Cyano-2-hydroxy-6-[1′-[(methylsulfonyl)oxy]-2′-hydroxy-2′-methylpropyl]tetrahydropyran (23). A solution of silyl mesylate **22** (10 g, 24.6 mmol) in acetonitrile (120 mL) and 49% hydrofluoric acid (12 mL) was stirred at room temperature for 24 h. The mixture was extracted with dichloromethane (3 × 100 mL), washed with water (2 × 50 mL) and brine (2 × 100 mL), dried over anhydrous sodium sulfate, and evaporated. Column chromatography using ethyl acetate afforded a mixture of isomers **23** (6.4 g, 89%) (R_f 0.23 and 0.18, ether): $[\alpha]^{24}_D$ −24.7° (*c* 5.69, $CHCl_3$); IR (film) 3480, 2990, 2948, 2252, 1450, 1418, 1355, 1338, 1178, 965, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (1 H, H_2, br t), 3.16 (3 H, CH_3SO_2, s).

(1*R*,4*R*,5*R*,7*S*)-7-Cyano-3,3-dimethyl-4-[(methylsulfonyl)oxy]-2,9-dioxabicyclo[3.3.1]nonane (24). The mixture **23** (9.5 g, 32.4 mmol) was dissolved in dichloromethane (95 mL); dry benzene (90 mL) and *p*-toluenesulfonic acid (0.95 g) were added. The solution was refluxed for 3 h on a Dean–Stark trap. The product was diluted with dichloromethane (50 mL), washed with ice-cold 5% aqueous sodium bicarbonate solution (2 × 10 mL), water (2 × 50 mL), and brine (2 × 25 mL), and then dried over anhydrous sodium sulfate. Chromatography of the crude material allowed isolation of the major component **24** (R_f 0.66), which was crystallized by dissolving in dichloromethane (1 mL) and diluting with petroleum ether (60–80 °C) (20 mL) to give

colorless crystals (2.91 g, 33%): mp 95–96 °C; $[\alpha]^{24}_D$ +31.1 (*c* 3.09, $CHCl_3$); IR (KBr) 3000, 2968, 2928, 2228, 1442, 1353, 1328, 1219, 1190, 1170, 1117, 1021 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.32 (1 H, H_1, t, J = 2), 4.38 (1 H, H_4, d, $J_{4,5}$ = 2), 4.32 (1 H, H_5, dd, $J_{4,5}$ = 2, $J_{5,6eq}$ = 5), 3.30 (1 H, H_7, tt, J = 5, 12), 3.09 (3 H, CH_3SO_2, s), 2.21 (1 H, H_{6eq}, ddd, $J_{6eq,8eq}$ = 2, $J_{5,6eq}$ = 5, $J_{6eq,6ax}$ = 13), 2.13–2.01 (2 H, H_{8eq}, H_{6ax}, m), 1.84 (1 H, H_{8ax}, ddd, $J_{1,8ax}$ = 2, $J_{7,8ax}$ = 12, $J_{8ax,8eq}$ = 13), 1.49 (3 H, CH_3, s), 1.35 (3 H, CH_3, s). Anal. Calcd for $C_{11}H_{17}NO_5S$: C, 48.00; H, 6.18; N, 5.09. Found: C, 47.96; H, 6.13; N, 5.13.

(1*R*,4*S*,5*R*,7*S*)-7-Cyano-3,3-dimethyl-2,9-dioxatricyclo-[3.3.1.0^{4,7}]nonane (25). Dry ammonia (20 mL) was condensed in a 100-mL three-necked flask equipped with a gas inlet tube and a cold-finger condenser charged with dry ice–acetone. Potassium metal (50 mg, 1.2 mmol) in small pieces and a crystal of ferric nitrate were added, and the mixture was stirred until the blue color had disappeared. Anhydrous THF (20 mL) was added to the mixture, and excess ammonia was allowed to evaporate at room temperature. The bicyclic nitrile **24** (100 mg, 0.36 mmol) in THF (5 mL) was added over a period of 5 min under argon, and the mixture was refluxed for 3 h. The mixture was cooled and quenched by addition of ice water (10 mL). The aqueous layer was extracted several times with dichloromethane (3 × 20 mL) and dried over anhydrous sodium sulfate. The crude product was chromatographed with ether (R_f 0.76) to afford **25** (45 mg, 69%). Capillary GC indicated no other volatile compound was present. The tricyclic nitrile exhibited the following characteristics: $[\alpha]^{24}_D$ +69.1° (*c* 0.74, pentane); IR (film) 2972, 2940, 2865, 2232, 1465, 1452, 1385, 1365, 1345, 1315, 1228, 1180, 1155, 1082, 1045, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (1 H, H_1, br d, $J_{1,8ax}$ = 2.5), 4.53 (1 H, H_5, t, $J_{4,5}$ = $J_{5,6eq}$ = 4), 2.72 (1 H, H_4, dd, $J_{4,8ax}$ = 1, $J_{4,5}$ = 4), 2.48 (1 H, H_{8eq}, ddd, $J_{1,8eq}$ = 1.3, $J_{6eq,8eq}$ = 2.5, $J_{8eq,8ax}$ = 13), 2.47 (1 H, H_{6eq}, ddd, $J_{6eq,8eq}$ = 2.5, $J_{5,6eq}$ = 4, $J_{6eq,6ax}$ = 10.4), 2.45 (1 H, H_{8ax}, ddd, $J_{4,8ax}$ = 1, $J_{1,8ax}$ = 2.5, $J_{8ax,8eq}$ = 13.0), 2.07 (1 H, H_{6ax}, d, $J_{6ax,6eq}$ = 10.4), 1.34 (3 H, CH_3, s), 1.31 (3 H, CH_3, s); MS (70 eV) *m/e* (relative intensity) 179.2 (M^+·, 4) 164 (8), 152 (2), 151 (17), 136 (18), 120 (100), 113 (25), 112 (52), 108 (53.4), 85 (78.0), 83.1 (59), 81.1 (32), 80 (28); HRMS for $C_{10}H_{13}NO_2$, calcd 179.0947, found 179.0983.

(1*R*,4*S*,5*R*,7*S*)-3,3-Dimethyl-7-formyl-2,9-dioxatricyclo-[3.3.1.0^{4,7}]nonane (26). To a solution of the nitrile **25** (600 mg, 3.5 mmol) in anhydrous THF (50 mL) at −78 °C under argon atmosphere was added 1 M diisobutylaluminum hydride in hexane (6.7 mL, 6.0 mol). The solution was stirred for 0.5 h at −78 °C and allowed to warm to room temperature. The reaction was stirred for a total of 5 h, whereupon 6 M hydrochloric acid (40 mL) was added at 0 °C and the two-phase system was stirred vigorously for 1 h. The mixture was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with brine (40 mL) and dried over anhydrous sodium sulfate. Column chromatography with ether (R_f 0.6) afforded **26** (460 mg, 75%): $[\alpha]^{24}_D$ +61.5° (*c* 2.21, pentane); IR (film) 2962, 2920, 2858, 2708, 1708, 1460, 1445, 1380, 1360, 1336, 1338, 1218, 1172, 1108, 1075, 1035, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.58 (1 H, CHO, s), 5.23 (1 H, H_1, br d, J = 3.3), 4.58 (1 H, H_5, t, $J_{4,5}$ = 3.9), 2.57 (1 H, H_4, dd, $J_{4,8ax}$ = 1.3, $J_{4,5}$ = 3.9), 2.56 (1 H, H_{8eq}, ddd, $J_{1,8eq}$ = 0.8, $J_{6eq,8eq}$ = 2.4, $J_{8eq,8ax}$ = 13), 2.35 (1 H, H_{6eq}, ddd, $J_{6eq,8eq}$ = 2.4, $J_{5,6eq}$ = 3.3, $J_{6eq,6ax}$ = 10.4), 2.21 (1 H, H_{8ax}, ddd, $J_{4,8ax}$ = 1.3, $J_{1,8ax}$ = 3.3, $J_{8ax,8eq}$ = 13), 1.80 (1 H, H_{6ax}, d, $J_{6ax,6eq}$ = 10.4), 1.29 (3 H, CH_3, s), 1.09 (3 H, CH_3, s); MS (70 eV) *m/e* (relative intensity) 183.2 (0.4), 182.2 (M^+·, 4), 168 (12), 167 (100), 164 (5), 154 (11), 153 (14), 139 (31), 123 (42), 121 (44), 83.1 (78), 55.1 (65), 43.1 (70); HRMS for $C_{10}H_{14}O_3$, calcd 182.0943, found 182.0937.

(1*R*,4*S*,5*R*,7*R*)-3,3,7-Trimethyl-2,9-dioxatricyclo-[3.3.1.0^{4,7}]nonane (1). Hydrazine hydrate (100%, 0.1 g) was added to a solution of the tricyclic aldehyde **26** (60 mg, 0.33 mmol) and potassium hydroxide (0.1 g, 2.5 mmol) in triethylene glycol (5 mL), and the mixture was heated at 135 °C for 1 h. The reaction temperature was gradually raised to 210–230 °C, distilling off the excess N_2H_4 and some of the product. The remaining mixture was then refluxed for 3 h at 210 °C. The mixture was cooled, diluted with water (10 mL), and extracted with dichloromethane (2 × 50 mL). The extracts and distillate were combined and washed with 1 M hydrochloric acid (5 mL), water (20 mL), and brine (2 × 20 mL). The crude product in dichloromethane was dried with anhydrous sodium sulfate and was subjected to column chromatography using pentane–ether (3:1) to afford 1 (40 mg, 73%). Bulb-to-bulb vacuum distillation of a portion of this product (14 mg) provided (+)-1 (4 mg, bp 68 °C (5 torr)). Analysis by capillary GC revealed no other volatile material other than 1 was present, and its retention time was identical with that of racemic lineatin: $[\alpha]^{24}_D$ +79° (*c* 0.21, $CHCl_3$); lit.[8] $[\alpha]^{24}_D$ +66.3 ± 3.5° (*c* 3.1, $CHCl_3$); lit.[9] $[\alpha]^{21.5}_D$ +85.5° (*c* 1.1, $CHCl_3$); IR (film) 2980, 2938, 2878, 1470, 1435, 1378, 1375, 1368, 1348, 1318, 1245, 1225, 1210, 1185, 1172, 1125, 1102, 1078, 1018, 1004, 965, 908, 872, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.11 (1 H, H_1, br d, $J_{1,8ax}$ = 3.2), 4.51 (1 H, H_5, dd, $J_{5,6eq}$ = 3.1, $J_{4,5}$ = 4.2), 2.11 (1 H, H_{8ax}, ddd, $J_{4,8ax}$ = 1.2, $J_{1,8ax}$ = 3.4, $J_{8ax,8eq}$ = 12.8), 1.97 (1 H, H_{8eq}, ddd, $J_{1,8eq}$ = 0.8, $J_{6eq,8eq}$ = 2.4, $J_{8eq,8ax}$ = 12.8), 1.91 (1 H, H_4, dd, $J_{4,8ax}$ = 1.2, $J_{4,5}$ = 4.2), 1.75 (1 H, H_{6eq}, dt, $J_{6eq,8eq}$ = 3.1, $J_{6eq,6ax}$ = 10.2), 1.66 (1 H, H_{6ax}, d, $J_{6ax,6eq}$ = 10.2), 1.26 (3 H, CH_3, s), 1.19 (3 H, CH_3, s), 1.18 (3 H, CH_3, s); MS (70 eV) *m/e* (relative intensity) 168 (M^+·, 0.04), 153 (1.9), 140 (1.6), 126 (12.6), 125 (17.2), 113 (10.7), 111 (36.7), 109 (30.8), 107 (27.2), 97 (19.9), 96 (37.9), 91 (10.3), 85 (100.0), 84 (20.4), 83 (55.9), 81 (26.2), 79 (21.3), 69 (45.5), 67 (20.7), 57 (27.3), 56 (45.5), 55 (87.1), 53 (20.4), 43 (76.5), 42 (10.0), 41 (90.0); HRMS for $C_{10}H_{16}O_2$, calcd 168.1151, found 168.1136.

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