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# *De novo* synthesis of carbohydrates by stereoselective aldol reaction: L-cladinose*

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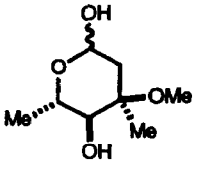
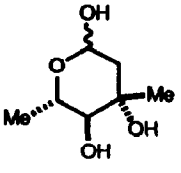
ABSTRACT

Aldol reactions of methyl 2-methoxypropanoate (**4**), the corresponding ester of 2-methoxypropanoic acid with 4-methyl-2,6-di-(*tert*-butyl)phenol (**13**), and silylketene acetals **14** and **15** with (*S*)-2-(phenylmethoxy)propanal (**17**) have been investigated. The lithium enolate of **4** reacts with **17** to give primarily β-hydroxy ester **18a**. If the reaction is carried out with the bis-silylketene acetal **14** under the influence of stannic chloride, β-hydroxy acid **20c** is produced. Compound **20c** is cleanly inverted, *via* the β-lactone **26**, to provide β-hydroxy acid **19c**. Compound **18a** has been converted into L-cladinose by the sequence of steps: **18a**→**35**→**39**→**40**→**41**→**42**→**1**.

In connection with an ongoing project aimed at efficient total synthesis of erythromycin A using stereocontrolled aldol reactions to establish relative stereochemistry,[2] we have investigated an aldol approach for *de novo* synthesis of cladinose, one of the two erythromycin A sugars. In this article, we report the full details‡ of this work, which resulted in a total synthesis of cladinose** (**1**) and the development of stereoselective aldol processes that could, in principle, be used for the synthesis of olivomycose (**2**) and the unnamed diastereomer[3,4] **3**.




**1**

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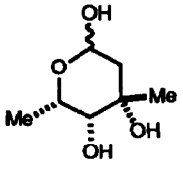


**3**

Our first approach was reaction of the lithium enolate of methyl 2-methoxypropanoate (**4**) with 2-(*tert*-butyldiphenylsilyl)oxypropanal (**5**, Scheme 1). This reaction gives a mixture of products from which a 5.7:1 mixture of aldols **6** and **7** can be isolated by preparative l.c. Aldols **6** and **7** are accompanied by variable amounts of a

* Paper 49 in the series "Acyclic Stereoselection". For paper 48, see ref. 1.
† To whom inquiries should be addressed.
‡ For a preliminary communication, see ref. 3.
** Ref. 4(a) records a recent synthesis of (–)-cladinose. For previous synthesis of cladinose and related branched-chain sugars, see ref. 4b.

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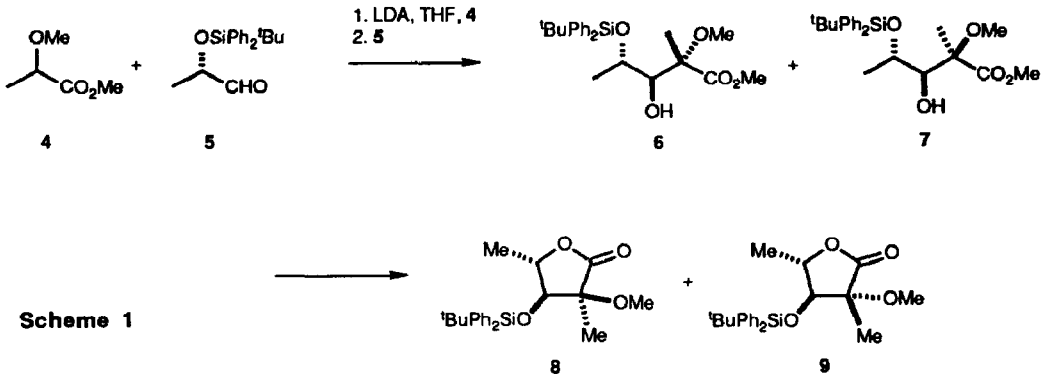


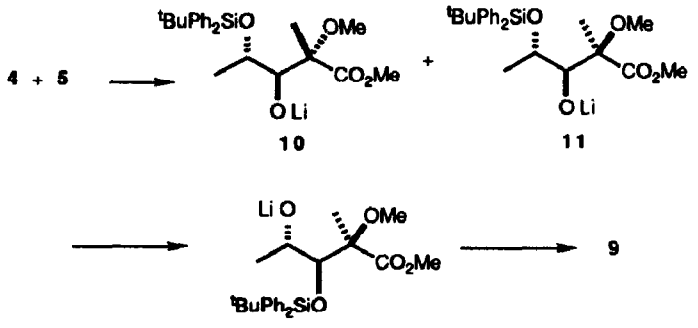

4 5 6 7 8 9

**Scheme 1**

less-polar product, shown by its i.r. stretch at 1780 $cm^{-1}$ and its mass spectrum to be a $\gamma$-lactone. Numerous methods for deprotection of aldol **6** were investigated and found to give only mixture of several products. However, treatment of the purified aldol with a catalytic amount of KF in *N,N*-dimethylformamide provides a crystalline $\gamma$-lactone (**8**, see later) in 87% yield. Notably, this $\gamma$-lactone is *different* ($^1$H-n.m.r.) from the one that is obtained as a by-product in the original aldol reaction. Furthermore, the initially formed lactone is an oil, whereas the one obtained by fluoride-catalyzed isomerization can be readily crystallized (m.p. 82–84°).

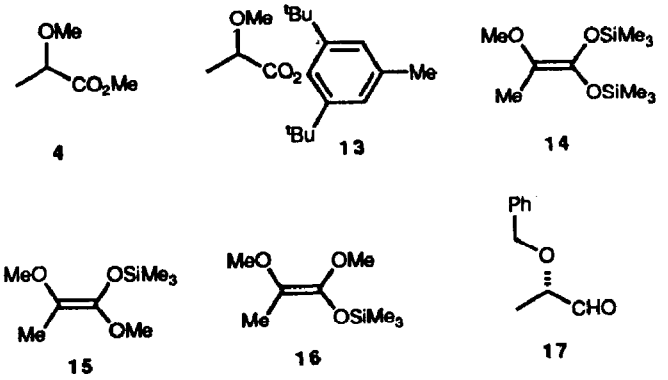
The foregoing results are consistent with the scenario depicted in Scheme 2. The aldol reaction of enolate of **4** with aldehyde **5** gives a mixture of aldolates **10** and **11**. Facile 1,2-silyl migration occurs from aldolate **11**, providing **12**. This substance then undergoes lactonization, with expulsion of lithium methoxide, to give lactone **9**, the oily $\gamma$-lactone. Intermediate **10** does not undergo the silyl transfer as readily as **11** because in the cyclic transition-state for the migration there is a steric interaction between the *cis*-alkyl groups, which increases the activation energy for the process. Because this preferential silyl migration and lactonization of one of the aldolates made precise evaluation of the aldol ratio difficult, we carried out the addition reaction and treated the crude aldol product directly with KF in DMF. Under these conditions, lactones **8** and **9** are obtained, presumably as a consequence of facile silyl migration under the reaction conditions, in a ratio of 3:1 (Scheme 1).

Although the major $\gamma$-lactone **8** has the desired relative stereochemistry, various attempts to homologate it failed, due to the reluctance of **8** or the derived hemiacetal to undergo ring-opening reactions. Thus, we turned our attention to approaches that would avoid the intervention of $\gamma$-lactone intermediates. To this end, reactions of several metal enolates and silyl ketene acetals derived from 2-methoxypropanonic acid with (*S*)-2-(phenylmethoxy)propanal (**17**, prepared from (*S*)-ethyl lactate[5]), were investigated. Nucleophilic species utilized in this study were ester **4**, the corresponding ester of 4-methyl-2,6-di(*tert*-butyl)phenol ("butylated hydroxytoluene", BHT),[6] the 1,1-bis(trimethylsilyl)ketene acetal[7] **14**, and the trimethylsilylketene acetal **15**. Compound **15** was prepared by treatment of **4** with a base, followed by reaction of the resulting enolate with chlorotrimethylsilane. The ratio of **15** and its *E* isomer **16** is



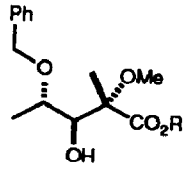

**Scheme 2**

dependent on the base used in the deprotonation. With lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF, or with lithium diisopropylamide (LDA) in a mixture of THF and hexamethylphosphoric triamide (HMPA) the **15**:**16** ratio is 7:1, LDA in pure THF gives a **15**:**16** ratio of 11:1, and lithium hexamethyldisilazane (LHMDS) in THF provides, within the limits of analysis, only the *Z* silylketene acetal* **15**.




Aldol reactions of **17** were investigated with the lithium, magnesium, and zirconium enolates of ester **4**, with the lithium enolate of ester **13**, and with silylketene acetals **14** ($BF_3$ or $SnCl_4$ catalysis) and **15** ($BF_3$ catalysis). Depending on the conditions, various mixtures of *β*-hydroxy esters or *β*-hydroxy acids **18**–**21** were produced. Results are summarized in Table I. The enolates of ester **4** give in each case a predominance of the product derived from Felkin-*syn* addition to **17**. With the lithium and zirconium enolates, the Felkin addition products **18a** and **19a** are formed in a nine-fold excess over the non-Felkin products **20a** and **21a**, whereas the magnesium enolate gives more of the chelation-controlled products **20a** and **21a**. The lithium enolate of BHT ester **13** gives, as expected,[5] more of the *anti* aldol **19b**, but the overall ratio of aldols is not preparatively useful.

* The *Z* enolate that leads to **15** is presumably more stable than the *E* enolate that leads to **16** because in the former the lithium cation can be chelated by the enolate and *α*-methoxy oxygens. This difference in product stability is expressed more strongly in the latter, more product-like transition states resulting from deprotonation of **4** with the less basic LHMDS.

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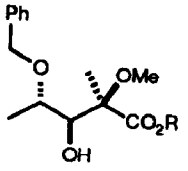


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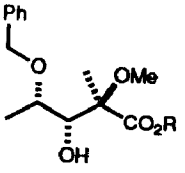


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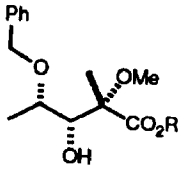


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a: R = Me b: R = BHT c: R = H

TABLE I

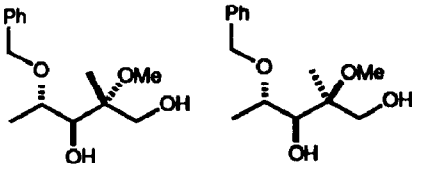
Stereochemistry of reaction of (*S*)-2-benzyloxypropanal with esters **4** and **13** and ketene acetals **14** and **15**

| *Reactant* | *Conditions* | *Product composition,(%)* | | | | |
|---|---|---|---|---|---|---|
| | | *R* | **18** | **19** | **20** | **21** |
| 4 | Li Enolate[a] | Me | 70 | 23 | 7 | 0 |
| 4 | Li Enolate[b] | Me | 63 | 21 | 17 | 0 |
| 4 | Li Enolate[c] | Me | 66 | 25 | 8 | 0 |
| 4 | Mg Enolate[d] | Me | 50 | 16 | 16 | 16 |
| 4 | Zr Enolate[e] | Me | 47 | 40 | 13 | 0 |
| 13 | Li Enolate[a] | BHT | 25 | 61 | 14 | 0 |
| 14 | $BF_3.OEt_2$[f] | H | 20 | 30 | 30 | 20 |
| 14 | $SnCl_4$ | H | 0 | 0 | 95 | 5 |
| 15 | $BF_3.OEt_2$[f] | Me | 0 | 0 | 67 | 33 |

[a] Enolate formed with LDA at −78° [b] Enolate formed with LDA at −100° [c] Enolate formed with LHMDS at −78° [d] Enolate formed with bis(cyclohexyl)aminomagnesium bromide at −78° [e] Enolate formed by addition of bis(cyclopentadienyl)zirconium dichloride to the lithium enolate at −78° [f] Reaction carried out by addition of 1.0 mole-equivalent of the indicated Lewis acid to a solution of the aldehyde in $CH_2Cl_2$ at −78°, followed by addition of the silylketene acetal.

Boron trifluoride-mediated reaction of a 11:1 mixture of ketene acetals **15** and **16** with aldehyde **17** gives a 1:1 mixture of the *syn* and *anti* aldols resulting from chelation-controlled addition. The same catalyst causes the bis(trimethylsilyl)ketene acetal **14** to react with **17** in an almost stereorandom manner to give *β*-hydroxy acids **18c–21c**. However, with stannic chloride, silylketene acetal **14** and aldehyde **17** undergo a highly stereoselective reaction, providing aldols **20** and **21** in a ratio of 19:1.

Correlation between the methyl ester and acid series of compounds was ac-



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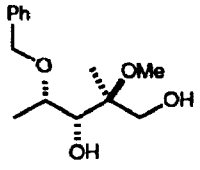

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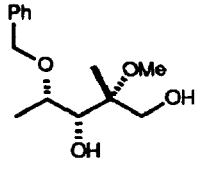
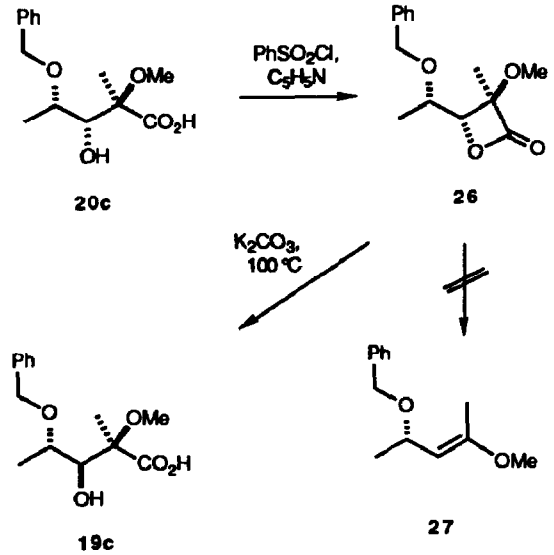


25

complished by reduction of the esters **18a–21a** and carboxylic acids **18c–21c** with lithium aluminium hydride to give the 1,3 diols **22–25**.

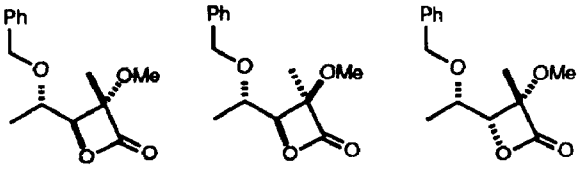
The relative stereochemistry of the four $\beta$-hydroxy acids is shown by the following series of experiments. Isomer **20c**, the major product from the $SnCl_4$-mediated reaction of silylketene acetal **14** with **17**, was converted into $\beta$-lactone **26** by treatment with benzenesulfonyl chloride in pyridine (Scheme 3). $\beta$-Lactone formation is known to involve ring closure by attack of the $\beta$-hydroxyl on the activated acyl group to give the lactone with retention of all stereochemistry[8]. Upon heating with potassium carbonate to effect stereospecific decarboxylation and formation of the enol ether[9] **27**, only



**Scheme 3**

β-hydroxy acid **19c** was obtained. Since the stereochemistry of saponification of α- and β-lactones is well established,[10] we can be sure that **19c** and **20c** are epimeric at the β-hydroxy position.

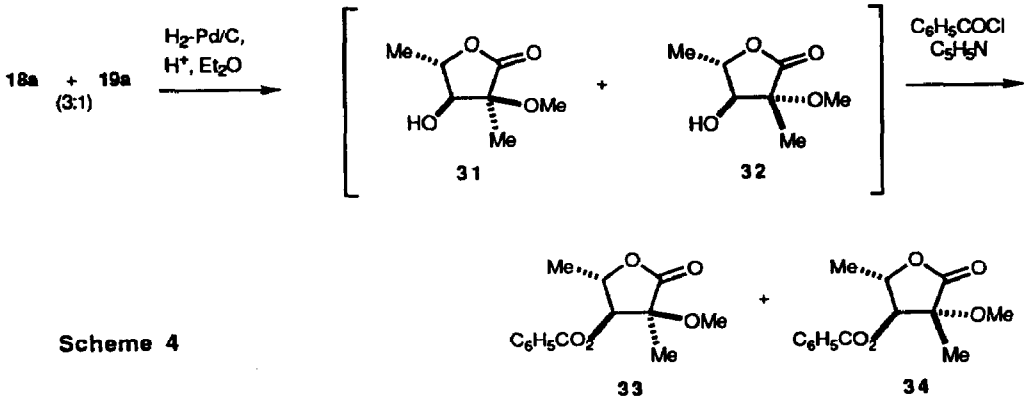
In a similar manner, β-hydroxy acids **18c**, **19c**, and **21c** were converted into β-lactones **28**, **29**, and **30**. Nuclear Overhauser enhancement experiments on lactone **26** and **28–30** provided evidence with regard to the relative stereochemistry at C-2 and C-3. Selective irradiation of the methyl singlets of lactones **26** or **28** caused enhancement of the resonances of the γ-methine proton and of the methoxy group, showing that **26** and **28** are derived from the *syn* β-hydroxy acids **20c** and **18c**. Irradiation of the methyl singlets in the isomeric lactones **29** and **30** caused enhancement of the β-methine protons, indicating that these lactones are derived from the *anti* β-hydroxy acids **19c** and **21c**.




**28** **29** **30**

Although the foregoing n.O.e. experiments define the relative stereochemistry of the four β-hydroxy acids at the α and β positions, they do not give any indication of the relative stereochemistry at the β and γ positions. To illuminate this point, γ-lactones **33–34** were synthesized from β-hydroxy esters **18a** and **19a** respectively (Scheme 4). A 3:1 mixture of **18a** and **19a** was hydrogenolyzed over palladium to give β-hydroxy-γ-lactones **31** and **32**. The crude mixture was treated with benzoyl chloride in pyridine to obtain the separable β-benzoyl-γ-lactones **33** and **34**.

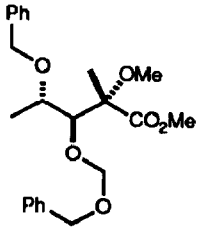
Selective irradiation of the α or γ-methyl groups in compound **33** caused enhancement of the β-methine hydrogen. Irradiation of the γ-methyl group in lactone **34** resulted in enhancement of the β-proton whereas irradiation of the α-methyl group showed no



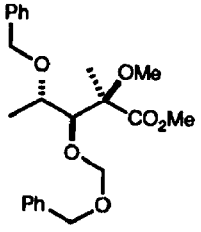

**Scheme 4**

β-proton enhancement. Both **33** and **34** must be derived from the Felkin aldols; *e.g.*, from β-hydroxy acids **18c** and **19c**. The n.O.e. experiments on lactones **26**, **28–30**, and **33–34**, coupled with the previously observed inversion of β-lactone **26** to form carboxylic acid **19c** upon saponification provides unambiguous proof of the relative stereochemistry of all of the aldols and β-hydroxy acids.

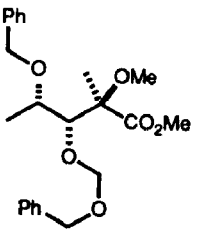
For the synthesis of L-cladinose, the best aldol ratio possible for the formation of β-hydroxy ester **18a** was obtained by using LDA in THF at −78°. The remaining problem to be faced in the synthesis was one-carbon homologation of the aldol. To this end, the free hydroxy groups of the 70:23:7 mixture of β-hydroxy esters **18a–20a** were protected with benzyloxychloromethane to give the benzyloxymethyl ethers[11] **35–37**. Chromatographic separation on silica gel allows isolation of the Felkin-*anti* isomer **36**, but the major and minor *syn* isomers, **35** and **37**, co-elute.




**35**




**36**

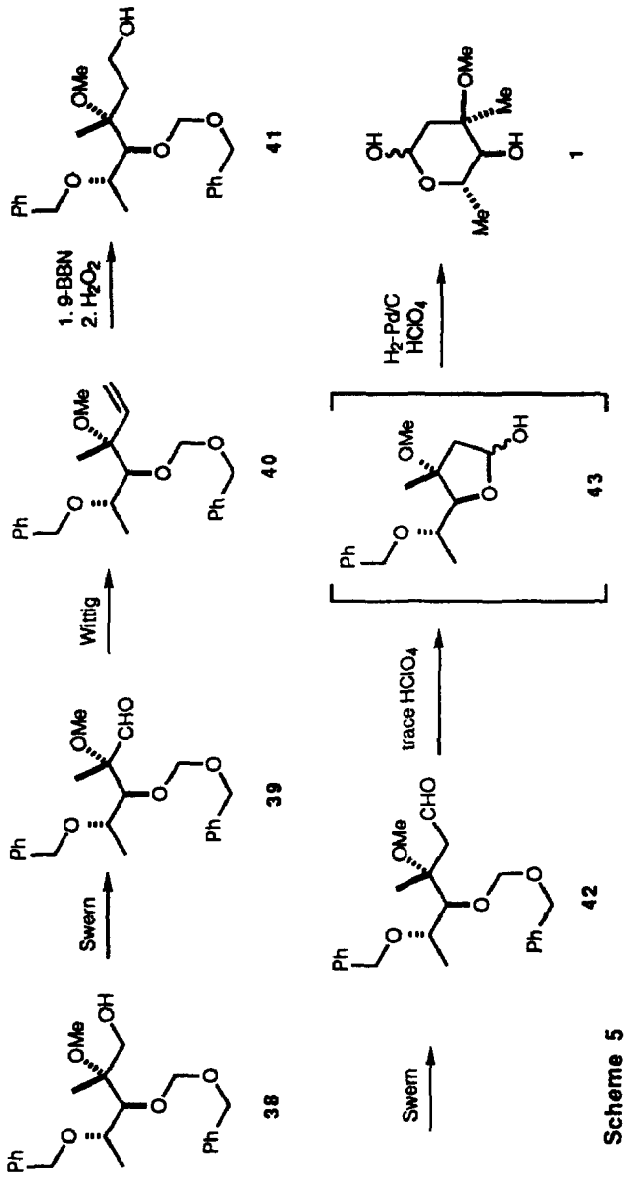



**37**

The crude 2-benzyloxymethoxy esters **35–37** were reduced with lithium aluminum hydride (Scheme 5). The easily separable alcohol **38** was obtained in 55% yield based on 2-benzyloxypropanal from a 70:22:8 ratio of aldol products **18a–21a**. Oxidation of alcohol **38** by the Swern method[12] provides aldehyde **39** in 95% yield. Wittig methylenation[13] of aldehyde **39** in THF affords alkene **40** in 95% yield. Hydroboration–oxidation of the terminal alkene with 9-borabicyclononane[14] followed by peroxide provides primary alcohol **41**, uncontaminated by possible secondary alcohols, as judged by $^1$H-n.m.r. spectroscopy. Swern oxidation[12] provides the homologated aldehyde **42**.

When the *bis*-protected cladinose **42** is treated in ethyl acetate with palladium on carbon under an atmosphere of hydrogen, no hydrogenolysis occurs. However, addition of minute traces of perchloric acid results in immediate transformation to the cyclic hemiacetal **43**. If more perchloric acid and fresh palladium on carbon was added under conditions in which lactol **43** had formed, the immediate uptake of two equivalents of hydrogen occurred and L-cladinose was isolated in 83% yield, identical by $^1$H-n.m.r. and i.r. spectroscopy with a sample isolated from erythromycin[15].

In conclusion, there are four diastereomeric relationships within the mycarose family of carbohydrates, exemplified by the structures **18–21**. In this study, we have found that stereocontrolled aldol reactions of 2-benzyloxypropanal can provide convenient access to three of these stereostructural forms, the 2-*C*-methylribitol series **18** (from the lithium enolate of ester **4**, the 2-*C*-methyllyxitol series **20** (from $SnCl_4$-mediated reaction of the silylketene acetal 14), and the 2-*C*-methylarabinitol series **19**


Swern
Wittig
1. 9-BBN
2. H2O2
Swern
trace HClO4
H2-Pd/C
HClO4
38
39
40
41
42
43
1

Scheme 5

(from C-3 inversion of **20**, *via* the *β*-lactone **26**). The utility of this methodology has been demonstrated by conversion of the 2-*C*-methylribitol intermediate into L-cladinose. Although such a demonstration has not been carried out, related methodology could, in principle, be used for the synthesis of L-olivomycose (**2**) and the unnamed diastereomer **3**.

## EXPERIMENTAL

*General methods.* — Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium–benzophenone immediately prior to use. *N*,*N*-Dimethylformamide (DMF), hexamethylphosphoric triamide (HMPA), and pyridine were distilled from $CaH_2$ and stored over 4Å molecular sieves. Unless otherwise noted, solvents were removed from organic extracts under vacuum with a rotary evaporator. All reactions involving organometallic reagents were conducted under an $N_2$ atmosphere. I.r. spectra were measured in $CHCl_3$ solution unless otherwise noted. $^1$H-n.m.r. spectra (220 or 250 MHz) and $^{13}$C-n.m.r. spectra (50 or 75 MHz) were determined in $CDCl_3$ solution. Mass spectra were obtained at 70 eV; data are tabulated as *m/z* (intensity expressed as percent of total ion current). Gas–liquid partition chromatography (g.l.c.) was done with SE-30 columns. Analytical thin-layer chromatography (t.l.c.) was performed with Analtech 250-*μ*m silica gel plates. Column and flash[16] chromatography were done with Silica Gel 60 Merck (70–230 and 230–400 mesh, respectively). High-performance liquid chromatography (h.p.l.c.) was done with *μ*-Porasil analytical and semi-preparative columns.

*Ethyl 2-[(1,1-dimethylethyl)diphenylsilyl]oxypropanoate*: — To a solution of ethyl lactate (7.08 g, 60 mmol) in 60 mL of DMF was added imidazole (8.16 g, 120 mmol) and *tert*-butylchlorodiphenylsilane[17] (15 mL, 60 mmol). After standing at room temperature overnight, the mixture was poured into a mixture of water and petroleum ether (150 mL each). The layers were separated and the aq. phase was extracted with petroleum ether. The combined organic phases were washed with 150 mL of the following solutions: $H_2O$, 5% HCl, $H_2O$, $NaHCO_3$, and NaCl. The solution was dried ($MgSO_4$), evaporated and the residue was distilled (Kugelrohr, 140°, 0.25 torr) to give 19.37 g (91%) of the protected ester; $\nu_{max}^{film}$ 3070, 2940, 2860, 1755, 1590, 1460, 1430, 1370, 1270, 1195, 1140, 1110, 1060, 1025, 975, 825, 745, 710, 700, and 695 cm$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.10 (s, 9 H), 1.11 (t, 3 H, *J* 7 Hz), 1.33 (d, 3 H, *J* 7 Hz), 3.93 (q, 2 H, *J* 7 Hz), 4.20 (q, 1 H, *J* 7 Hz), 7.32 (m, 6 H), and 7.50 (m, 4 H).

*Anal.* Calc. for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 71.01; H, 7.92.

*2-[(1,1-Dimethylethyl)diphenylsilyl]oxypropanal* (**5**). — The foregoing ester (3.57 g, 10 mmol) was dissolved in 15 mL of anhydrous ether and cooled to −100° with a liquid $N_2$–ether bath. Diisobutylaluminum hydride (20 mL of a 5M solution in hexane) was added dropwise over ~5 min. After stirring for 1.5 h at −100°, the solution was rapidly poured into 60 mL of 5 M HCl and stirred until gas evolution ceased (~5 min). The layers were separated and the aq. phase extracted with ether. The combined organic

phases were washed with 1% HCl solution until they were no longer cloudy, and were then washed with brine. The solution was dried ($MgSO_4$), filtered through a pad of Celite, and evaporated. The residue was distilled (Kugelrohr, 145°, 0.5 torr) to yield 2.85 g (91%) of the aldehyde; $\nu_{max}^{film}$ 3070, 2960, 2940, 2860, 1740, 1590, 1460, 1425, 1375, 1105, 1005, 960, 825, 745, 710, 705, and 695 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.10 (s, 9 Hz), 1.20 (d, 3 H, *J* 7 Hz), 4.00 (d, 1 H, *J* 1,7 Hz), 7.33 (m, 6 H), 7.52 (m, 4 H), and 9.50 (d, 1 H, *J* 1 Hz).

*Anal.* Calc. for $C_{19}H_{24}O_2Si$: C, 73.03; H, 7.74. Found: C, 73.08; H, 7.80.

*Aldol addition of ester* **4** *to aldehyde* **5** *and conversion into lactone* **8**: — To a solution of LDA (7.58 mmol, prepared from 1.10 mL of diisopropylamine and 5.00 mL of 1.50M BuLi in hexanes) in 40 mL of THF was added methyl 2-methoxypropanoate (0.73 mL, 6.67 mmol) at −70°. After stirring the solution for 30 min at low temperature, 6.67 mmol of aldehyde 5 was added, followed by 20 mL of saturated $NH_4Cl$ solution. The mixture was warmed to room temperature, the layers were separated, and the aq. phase was extracted with ether (2 × 50 mL). Washing with 1% HCl and brine, drying, filtration, and removal of solvents under diminished pressure gave 1.78 g (62%) of a 6:1 ratio of β-hydroxy esters **6** and **7**, after preparative h.p.l.c. (20 ether–hexane, $R_F$ 0.15).

*Methyl (2S,3*S*,4*S*)-3-hydroxy-2-methyl-2-methoxy-4-[(1,1-dimethylethyldiphenylsilyl)oxy]pentanoate* (**6**). — $\nu_{max}^{film}$ 3500, 1740, 1425, 1377, 1255, 1180, 1110, 1050, 980, 820, 740, and 710$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.03 (s, 9 H), 1.16 (d, 3 H, *J* 7 H), 1.40 (s, 3 H), 3.16 (s, 3 H), 3.43 (s, 3 H), 7.33 (m, 6 H), and 7.50 (m, 4 H); $^{13}$C-n.m.r.: $\delta$ 17.5, 17.9, 26.9, 51.5, 51.8, 70.5, 79.3, 127.4, 129.4, 135.7, and 172.7.

*Anal.* Calc. for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 66.86; H, 8.06.

The purified aldol (770 mg, 1.79 mmol) was dissolved in 6 mL of DMF and anhydrous KF (10 mg, 0.17 mmol) was added. The solution was heated for 20 min at 60°, cooled, and partitioned between water and petroleum ether. The organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Column chromatography (20% ether–hexane, $R_F$ 0.32) gave 556 mg (87%) of the lactone, which crystallized on standing (mp 82–84°, hexane).

*(3R,4S,5S)-3,5-Dimethyl-3-methoxy-4-{[(1,1-dimethylethyl)diphenylsilyl]oxy}-tetrahydrofuran-2-one* (**8**). — $\nu_{max}^{film}$ 3050, 2940, 2860, 1780, 1590, 1425, 1380, 1305, 1220, 1190, 1145, 1105, 1040, 880, 820, 745, and 710 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.10 (1 s, 2 H), 1.13 (d, 3 H, *J* 7 Hz), 3.33 (s, 3 H), 3.43 (d, 1 H, *J* 7 Hz), 4.43 (quintet, 1, *J* 7 Hz), 7.35 (m, 6 H), and 7.50 (m, 4 H).

*Anal.* Calc. for $C_{23}H_{30}O_4Si$: C, 69.31; H, 7.54. Found: C, 69.10, H, 7.74.

Alternatively, the two reactions could be performed consecutively (7 mmol scale) to provide in 63% overall yield a 3:1 mixture of lactones which were separable by preparative h.p.l.c. (10% ether–hexane, $R_F$ (major) 0.23, $R_F$ (minor) 0.17.

*Ketene acetal* **14**: — A solution of LDA was prepared by adding 201.6 mL of 1.50 M butyllithium in hexanes (0.302 mol) to a solution of 35.94 g (0.355 mol) of diisopropylamine in 200 mL of THF at 5°. After recooling the LDA solution to 7°, a solution of 14.31 g (0.137 mol) of 2-methoxypropanoic acid in 75 mL of THF was added and the solution was allowed to warm to room temperature. After 1 h 43.61 mL (37.33 g, 0.344 mol) of chlorotrimethylsilane was added and the resulting pink solution was stirred

overnight. The THF solution was extracted with water (3 × 150 mL), brine (150 mL), and concentrated under diminished pressure to obtain 50 mL of liquid residue. This material was distilled to give 10.0 g (55%) of ketene acetal **14**; $\nu_{max}^{film}$ 1720, 1250, 1225, 1145, and 840 $cm^{-1}$; $^1$H-n.m.r.: 0.18 (s, 9 H), 0.20 (s, 9 H), 1.72 (s, 3 H), and 3.40 (s, 3 H).

*Anal.* Calc. for $C_{10}H_{24}O_3Si_2$: C, 48.34; H, 9.74. Found: C, 48.53; H, 9.75.

(Z)-*[(1,2-Dimethoxy-1-propenyl)oxy]trimethylsilane* (**15**, RN 92817-38-4) and (E)-*[(1,2-dimethoxy-1-propenyl)oxy]trimethylsilane* (**16**, RN 92818-02.5): — To a solution of LDA (5.34 mmol) in 12 mL of THF at −78° was added a solution of 551 mg (4.67 mmol) of ester **4** in 5 mL of THF. After stirring for 3 min, 0.70 mL (5.52 mmol) of chlorotrimethylsilane was added. The solution was warmed to room temperature over 30 min, and the solvents were removed under diminished pressure. The resulting residue was taken up in ether and filtered to remove the LiCl. Removal of the ether under diminished pressure gave 628 mg (70%) of ketene acetal as an approximate 12:1 mixture of diastereomers. This material was relatively unstable and decomposed upon attempted distillation at 40° with a Kugelrohr apparatus (bath temperature 0.125 torr). Spectra were obtained with crude material, obtained directly from the foregoing procedure; $\nu_{max}$ (mixture of diastereomers): 1260 and 855 $cm^{-1}$.

*Major isomer* **5** $^1$H-n.m.r.: $\delta$ 0.23 (s, 9 H), 1.71 (s, 3 H), 3.40 (s, 3 H), and 3.43 (s, 3 H); $^{13}$C-n.m.r.: $\delta$ −0.1, 11.3, 56.0, 56.5, 121.4, and 146.3.

*Minor isomer* **16** $^1$H-n.m.r.: $\delta$ 0.12 (s, 9 H), 1.71 (s, 3 H), 3.40, (s, 3 H), and 3.48 (s, 3 H); $^{13}$C-n.m.r.: $\delta$ −0.2, 12.3, 57.2, 57.7, 122.6, and 147.4.

*General procedure for the synthesis of methyl 4-benzyloxy-3-hydroxy-2-methoxy-2-methylpentanoate* (**18a–21a**). — To a solution of LDA (1.88 mmol, prepared from 0.27 mL of diisopropylamine and 1.25 mL of a 1.50M solution of BuLi in 10 mL of THF, at 0°), at −78°, was added 0.18 g (1.66 mmol) of methyl 2-methoxypropanoate (**4**) in 0.3 mL of THF. The syringe used to introduce the ester was rinsed with an additional 0.2 mL of THF. The solution was stirred for 30 min, at −78°, and 0.272 g (1.66 mmol) of (*S*)-(2-benzyloxy)propanal[4] (**17**) was added. To the stirring mixture was added, after 5 min, 5 mL of a saturated aqueous $NH_4Cl$ solution. The cooling bath was removed, and the stirring solution slowly warmed to room temperature. The layers were separated, and the aqueous fraction was washed with two 10-mL portions of ether. The combined organic fractions were washed with 1% aq. HCl, and brine. The organic fraction was dried over $MgSO_4$, and the solvents were removed to give the crude product.

*Procedure* A. Aldol addition as given in the foregoing general procedure provided the aldol products **18a**, **19a**, and **20a** in a 70:23:7 ratio, as judged from the $^1$H-n.m.r. spectrum, in 70% yield.

*Procedure* B. Aldol addition as given in the foregoing general procedure, except the temperature of the system during aldehyde addition was kept at −100° by means of an ether–liquid $N_2$ bath, provided in 65% yield the aldol products **18a**, **19a**, and **20a** in a 63:21:17 ratio as judged from the $^1$H-n.m.r. spectrum.

*Procedure* C. Aldol addition as given in the foregoing general procedure, except the diisopropylamine was replaced by an equivalent number of mmol of isopropylcyclohexylamine, provided the aldols **18a**, **19a** and **20a** in 65% yield as a 66:25:9 ratio as judged from the $^1$H-n.m.r. spectrum.

*Procedure* D. Aldol addition as given in the foregoing general procedure, except the base used for deprotonation was *N,N*-dicyclohexylaminomagnesium bromide (1.88 mL, 1.88 mmol), prepared as a 1.0M solution in THF from 0.82 g (4.52 mmol) of dicyclohexylamine and 1.60 mL (4.00 mmol) of a 2.50M solution of MeMgBr in diethyl ether in 3.50 mL of THF at 65°, at −50°, and the aldehyde was added at −30°. The aldol products **18a–21a** were obtained in 45% as a 50:16:16:16 ratio of diastereomers as judged from the $^1$H-n.m.r and $^{13}$C-n.m.r. spectra of the crude product.

*Procedure* E. Aldol addition as given in the foregoing general procedure, except that 55 mg (0.46 mmol) of ester **4** was added to 0.51 mmol of LDA in 4 mL of THF at −78°. To this stirring solution, at −78°, was added 148 mg (0.51 mmol) of bis-(cyclopentadienyl)zirconium dichloride in 3 mL of THF. The cooling bath was removed, and the system was warmed to 25° over a 30-min period. To this stirring solution, recooled to −78°, was added 83 mg (0.51 mmol) of aldehyde **17** in 0.5 mL of THF. To the stirring mixture after 1 h, at −78°, was added 8 mL of saturated aqueous $NH_4Cl$. The cooling bath was removed, and the system warmed to room temperature. The mixture was filtered through a Celite pad using $CH_2Cl_2$ as wash solvent. The layers were separated, and the organic fraction was washed with water, and brine. The solvents were removed to obtain 78 mg (60%) of the aldols **18a**, **19a**, and **20a** in a ratio of 47:40:13 as judged from the $^1$H-n.m.r. spectrum.

*Procedure* F. Under a $N_2$ atmosphere, into a 10 mL round-bottomed flask fitted with a magnetic stirring bar and a rubber septum was placed 200 mg (1.22 mmol) of aldehyde **17** in 10 mL of $CH_2Cl_2$. To this stirring solution, at −78°, was added 173 mg (0.15 mL, 1.22 mmol) of boron trifluoride etherate and a solution of 257 mg (1.11 mmol) of silylketene acetal **15** in 5 mL of $CH_2Cl_2$. The reaction solution was stirred for 1 h at −78°, and 5 mL of a saturated $NaHCO_3$ solution was added. The cooling bath was removed, and the mixture was slowly warmed to room temperature. The layers were separated, and the organic fraction was diluted with diethyl ether, and washed with water and brine. Solvents were removed to obtain 220 mg (70%) of the aldol products **20a** and **21a** in a 67:33 ratio as judged from the $^1$H-n.m.r. spectrum.

*Spectral and analytical data for aldol products* **18a–21a**. — *Methyl 4-O-benzyl-5-deoxy-2-C-methyl-2-O-methyl-4-L-ribonate* (**18a**). Purified by preparative analytical l.c. using 1:9 ether–hexanes as eluant to obtain a clear oil; $\nu_{max}$ 3550 and 1725 cm$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.27 (d, 3 H, $J$ 5.2 Hz), 1.51 (s, 3 H), 3.24 (d, 1 H, $J$ 5.2 Hz), 3.35 (s, 3 H), 3.42 (s, 3 H), 3.63 (m, 2 H), 4.32 (d, 1 H, $J$ 10.9 Hz), 4.47 (d, 1 H, $J$ 10.9 Hz), and 7.39 (m, 5 H); $^{13}$C-n.m.r.: $\delta$ 16.2, 18.5, 51.1, 70.4, 74.3, 77.6, 78.8, 81.6, 127.8, 127.9, 128.1, 138.1, and 172.7.

*Anal.* Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.11; H, 7.92.

*Methyl 4-O-benzyl-5-deoxy-2-C-methyl-2-O-methyl-L-arabinonate* (**19a**). Analytical data were obtained on a sample purified by preparative analytical l.c. using 1:9 ether–hexanes as eluant to obtain a clear oil; $\nu_{max}$ 3550 and 1730 cm$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.28 (d, 3 H, $J$ 6.4 Hz), 1.53 (s, 3 H), 2.95 (d, 1 H, $J$ 10.0 Hz), 3.32 (dd, 1 H, $J$ = 0.95, 10.0 Hz), 3.35 (s, 3 H), 3.38 (s, 3 H), 3.98 (dq, 1 H, $J$ = 1.0, 6.4 Hz), 4.55 (d, 1 H, $J$ 10.9 Hz), and 7.3 (m, 5 H); $^{13}$C-n.m.r.: $\delta$ 12.8, 51.3, 70.3, 74.4, 77.9, 79.1, 81.8, 138.6, and 172.0.

*Anal.* Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.02; H, 7.67.

*Methyl 4 -O-benzyl-5-deoxy-2-C-methyl-2-O-methyl-4-L-lyxonate* (**20a**). Analytical data were obtained on a sample of **20a** containing 33% of isomer **21a**. This sample had been purified by preparative l.c. using 1:6 ethyl acetate–hexanes as eluant to obtain a clear oil; $\nu_{max}$ 3570 and 1730 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.32 (d, 3 H, $J$ 6.7 Hz), 1.34 (s, 3 H), 2.58 (d, 1, $J$ 3.2 Hz), 3.24 (s, 3 H), 3.43 (s, 3 H), 3.50 (dq, 1 H, $J$ 8.1, 6.7 Hz), 3.89 (dd, 1 H, $J$ 3.1, 8.1 Hz), 4.28 (d, 1 H, $J$ 11 Hz), 4.52 (d, 1 H, $J$ 11 Hz), and 7.32 (m, 5 H), $^{13}$C-n.m.r.: $\delta$ 13.4, 16.3, 51.6, 70.6, 74.8, 78.1, 81.8, 127.5, 128.2, 128.9, 138.1, and 173.2.

*Anal.* Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.89; H, 7.82.

*Methyl 4-O-benzyl-5-deoxy-2-C-methyl-2-O-methyl-L-xylonate* (**21a**). $^1$H-n.m.r data were obtained on a sample containing 67% of the diastereomer **20a**: $\delta$ 1.28 (d, 3 H, $J$ 6.7 Hz), 1.54 (s, 3 H), 2.95 (br d, 1 H, $J$ 11.2 Hz), 3.33 (m, 2 H), 3.34 (s, 3 H), 3.39 (s, 3 H), 4.29 (d, 1 H, $J$ 11.0 Hz), 4.54 (d, 1 H, $J$ 11.0 Hz), and 7.30 (m, 5 H).

*Carboxylic acids* **18c–21c**. — *Procedure* A. To stirring solution, at 0°, of 272 mg (0.96 mmol) of esters **18a–21a** (70:23:7 ratio) in 1 mL of MeOH was added 57 mg (1.0 mmol) of KOH in 1 mL of water. The solution was stirred for 16 h, during which time the ice bath slowly expired. The MeOH was removed, and the residue partitioned between 30 mL of water and two 10-mL portions of diethyl ether. The aqueous was acidified to pH 1 (as judged by pHydrion paper) with 10% aqueous HCl, and extracted with four 10-mL portions of $CH_2Cl_2$. The combined $CH_2Cl_2$ fractions were dried over $NgSO_4$, and the solvent was removed to obtain 211 mg (82%) of the carboxylic acids **18c**, **19c**, and **20c** (70:23:7 ratio by $^1$H-n.m.r.) as a waxy, white solid, m.p. 74–84°. Analytical data were obtained on this mixture of diastereomers.

*Procedure* B. To a stirring solution, at −78°, of 0.57 mL (1.27 g, 4.87 mmol) of $SnCl_4$ in 50 mL of $CH_2Cl_2$ was added 0.800 g (4.87 mmol) of aldehyde **17** over a 30-s period. After 5 min 1.46 g (5.35 mmol) of ketene acetal **14** was added. The mixture was stirred for 15 min and 5 mL of saturated aq. $NaHCO_3$ was added. The mixture was taken up in 75 mL of $CH_2Cl_2$ and the organic fraction was washed with three 25-mL portions of water. The organic fraction was washed with brine, dried over $Na_2SO_4$, and the solvent removed to obtain 1.21 g (93%) of carboxylic acids **20c** and **21c** in a 19:1 ratio as judged by $^1$H-n.m.r.

*Procedure* C. The previous procedure was followed except that 0.63 mL (0.73 g, 4.9 mmol) of boron trifluoride etherate was used instead of $SnCl_4$. The carboxylic acids **18c-21c** were obtained as a yellow oil in a 2:3:3:2 ratio as judged by $^1$H-n.m.r.

*Spectral data for carboxylic acids* **18c-21c**. — *4-O-Benzyl-5-deoxy-2-C-methyl-2-O-methyl-4-L-ribonic acid* (**18c**). Data were obtained on a sample containing 23% of isomer **19c** and 7% of isomer **20c**; $\nu_{max}$ 3560, 3000 (br), 1770, and 1745 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.26 (d, 3 H, $J$ 6.2 Hz), 1.50 (s, 3 H), 3.41 (s, 3 H), 3.65 (dq, 1 H, $J$ 6.4, 6.4 Hz), 3.84 (d, 1 H, $J$ 6.6 Hz), 4.48 (dd, 2 H, $J$ 11.5, 19.6 Hz), and 7.33 (m, 5 H).

*4-O-Benzyl-5-deoxy-2-C-methyl-2-O-methyl-L-arabinonic acid* (**19c**). Data were obtained on a sample containing 30% of isomer **18c**; $\nu_{max}$ 3530, 3000 (br), 1780, 1735, 1720, and 1710 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.26 (d, 3 H, $J$ 5.7 Hz), 1.38 (s, 3 H), 3.05 (br s, 2 H), 3.30 (s, 3 H), 3.65 (m, 1 H), 3.75 (m, 1 H), 4.44 (d, 1 H, $J$ 11.5 Hz), 4.57 (d, 1 H, $J$ 11.5 Hz), and 7.33 (m, 5 H).

*4-O-Benzyl-5-deoxy-2-C-methyl-2-O-methyl-L-lyxonic acid* (**20c**). Data were obtained on a sample containing 5% of isomer **21c**; $\nu_{max}$: 3550, 1740, and 1650 $cm^{-1}$; $^1$H-n.m.r.: 1.28 (d, 3 H, *J* 6.1 Hz), 1.41 (s, 3 h), 3.33 (s, 3 H), 3.68 (d, 1 H, *J* 3.1 Hz), 3.74 (dq, 1 H, *J* 3.1, 6.1 Hz), 4.43 (d, 1 H, *J* = 11.4 Hz), 4.60 (d, 1 H, *J* 11.3 Hz), and 7.33 (m, 5 H).

*4-O-Benzyl-5-deoxy-2-C-methyl-2-O-L-ribonic acid* (**21c**). Data were obtained on a sample containing 95% of isomer **20c**; $^1$H-n.m.r. (partial): $\delta$ 1.33 (d, 3 H, *J* 6.1 Hz), and 3.36 (s, 3 H).

*General procedures of $LiAlH_4$ reduction of aldols* **18–21**. — To a solution of 76 mg (2.0 mmol) of $LiAlH_4$ in 4.0 mL of dry THF or ether, at 0°, was added a solution of 1.0 mmol of aldol in 4.0 mL of the same solvent. The mixture was stirred for 2 h at room temperature, and then quenched and worked up by the Fieser method[18] to obtain the crude product. An analytical sample was prepared from a mixture of diol isomers.

*Anal.* Calc. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.09; H, 8.76.

*Procedure* A. The general procedure was followed using 38.0 mg (1.00 mmol) of $LiAlH_4$ and 188.4 mg (0.667 mmol) of aldol esters **18a**, **19a**, **20a** (70:23:7 ratio) in THF. The solvents were removed to afford 116.5 mg (68%) of diols **22**, **23**, **24** (70:23:7 ratio) as a colorless oil; $\nu_{max}$ 3530, 1060 $cm^{-1}$.

*Procedure* B. The general procedure was followed using 212.4 mg (5.59 mmol) of $LiAlH_4$ and 750 mg (2.80 mmol) of carboxylic acids **20c** and **21c** (19:1 ratio) in 10 mL of ether. The solvents were removed to afford 560 mg (79%) of diols **24** and **25** in a 95:5 ratio as judged from the $^1$H-n.m.r. spectrum; $\nu_{max}$ 3550 and 1075 $cm^{-1}$.

*Procedure* C. To a solution of 0.75 mmol of LDA in 2 mL of THF at −78° was added a solution of 208 mg (0.68 mmol) of BHT ester **13** in 0.5 mL of THF. To the stirring solution, at −78°, after 1 h, was added 118 mg (0.72 mmol) of aldehyde **17**. The mixture was stirred for 15 min, and 5.0 mL of saturated aq. $NH_4Cl$ was added. Following the standard workup procedure given for aldol products **18a–20a** afforded 339 mg (105%) of the BHT aldols as a colorless oil.

The general procedure for the reduction of aldol products was followed using 265 mg (6.8 mmol) of $LiAlH_4$ and 300 mg of the crude BHT aldols in 1.5 mL of THF. Following the standard workup and column chromatography using 1:1 EtOAc–hexane as eluant afforded 32.5 mg (20%) of the diols **22**, **23**, **24** in the ratio of 24:61:15 as judged from the $^1$H-n.m.r. spectra of the crude and purified mixture; $\nu_{max}$ 3550 and 1075 $cm^{-1}$.

*2-O-Benzyl-1-deoxy-4-C-methyl-4-O-methyl-D-ribitol* (**22**). — Flash chromatography of a sample containing isomers **22**, **23** and **24**, using 1:2 EtOAc–hexane as eluant, afforded the least polar compound, diol **22**, as a colorless oil; $^1$H-n.m.r.: $\delta$ 1.23 (s, 3 H), 1.34 (d, 3 H, *J* 6.2 Hz), 2.62 (t, 1 H, *J* 6.3 Hz), 2.72 (d, 1 H, *J* 5.2 Hz), 3.29 (s, 3 H), 3.60 (m, 2 H), 3.65 (t, 1 H, *J* 5.1 Hz), 3.77 (dq, 1 H, *J* 6.1, 6.1 Hz), 4.44 (d, 1 H, *J* 11.3 Hz), 4.64 (d, 1 H, *J* 11.3 Hz), and 7.33 (m, 5 H).

*2-O-Benzyl-1-deoxy-4-C-methyl-4-O-methyl-D-arabinitol* (**23**). — Analytical data were obtained on the purified sample prepared by foregoing procedure *C*; $^1$H-n.m.r.: $\delta$ 1.02 (s, 3 H), 1.36 (d, 3 H, *J* 6.0 Hz), 2.67 (d, 1 H, *J* 2.7 Hz), 2.85 (t, 1 H, *J* 7.4 Hz), 3.31 (s, 3 H), 3.63 (m, 3 H), 3.75 (dd, 1 H, *J* 6.9 Hz), 4.39 (d, 1 H, *J* 11.2 Hz), 4.65 (d, 1 H, *J* 11.2 Hz), and 7.34 (m, 5 H).

*2-O-Benzyl-1-deoxy-4-C-methyl-4-O-methyl-D-lyxitol* (**24**). — Analytical data were obtained on a sample containing 95% of isomer **24** and 5% of isomer **25** as a light-yellow oil; $^1$H-n.m.r.: $\delta$ 1.20 (s, 3 H), 1.33 (d, 3 H, $J$ 6.0 Hz), 2.84 (t, 1 H, $J$ 6.3 Hz), 2.94 (d, 1 H, $J$ 5.2 Hz), 3.28 (s, 3 H), 3.58 (m, 2 H), 3.68 (dd, 1 H, $J$ 5.4, 5.4 Hz), 3.76 (dq, 1 H, $J$ 6.0, 6.0 Hz), 4.43 (d, 1 H, $J$ 11.4 Hz), 4.62 (d, 1 H, $J$ 11.4 Hz), and 7.32 (s, 5 H).

*2-O-Benzyl-1-deoxy-4-C-methyl-4-O-methyl-D-xylitol* (**25**). — Analytical data was obtained on a sample containing 95% of isomer **24** and 5% of isomer **25**. Partial $^1$H-n.m.r.: $\delta$ 1.10 (s, 3 H), 1.32 (d, 3 H, $J$ 6.2 Hz), and 3.28 (s, 3 H).

*General procedure for the synthesis of* $\beta$-lactones (**26**, **28–30**). — To a stirring solution of 0.268 g (1.00 mmol) of $\beta$-hydroxy acid (**18c–21c**) in 5 mL of pyridine, at 0°, was added 0.26 mL (0.354 g, 2.00 mmol) of benzenesulfonyl chloride. The mixture was stirred for 16 h, during which time the ice bath slowly expired. The solution was diluted with 75 mL of ether, and was extracted with four 25-mL portions of saturated $CuSO_4$ solution. The organic fraction was extracted with water and brine, and dried over $MgSO_4$. The organic solvents were removed to give pure samples of the $\beta$-lactones (**26**, **28–30**) as colorless oils (80–95% yield). Silica gel column chromatography using 1:19 ether–hexane as eluant was used to prepare samples for $^1$H-n.m.r. analysis (order of elution on silica gel **29**, **30**, **28**, **26**).

(*1'S,3R,4R*) *4-[1'-(benzyloxy)ethyl]-3-methoxy-3-methyloxetan-2-one* (**26**). — Prepared and isolated from a 19:1 mixture of acids **20c** and **21c**; $\nu_{max}$ 1835 and 1095 cm$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.24 (d, 3 H, $J$ 6.3 Hz), 1.47 (s, 3 H), 3.48 (s, 3 H), 3.75 (dq, 1 H, $J$ 8.5, 6.3 Hz), 4.54 (d, 1 H, $J$ 8.5 Hz), 4.65 (s, 2 H), and 7.34 (m, 5 H): $^{13}$C-n.m.r.: $\delta$ 14.4, 16.0, 53.0, 71.4, 72.8, 83.0, 89.0, 126.6, 127.5, 128.2, 137.8, and 170.1.

*Anal.* Calc. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.31; H, 7.23.

(*1'S,3S, 4S*)-*4-[1'-(benzyloxy)ethyl]-3-methoxy-3-methyloxetan-2-one* (**28**) Prepared and isolated as a colorless oil from a 70:23:7 mixture of acids **18c**, **19c**, **20c**; $\nu_{max}$ 1825 and 1135 cm$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.36 (d, 3 H, $J$ 6.2 Hz), 1.51 (s, 3 H), 3.44 (s, 3 H), 3.75 (dq, 1 H, $J$ 8.3, 6.2 Hz), 4.35 (d, 1 H, $J$ 8.3 Hz), 4.46 (d, 1 H, $J$ 11.4 Hz), 4.67 (d, 1 H, $J$ 11.4 Hz), and 7.33 (m, 5 H); $^{13}$C-n.m.r.: $\delta$ 14.1, 16.0, 53.0, 70.6, 72.2, 81.9, 89.7, 127.8, 127.9, 128.4, 137.4, and 169.8; $m/z$ calc. for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1210.

(*1'S,3R,4S*)-*4-[1'-(benzyloxy)ethyl]-3-methoxy-3-methyloxetan-2-one* (**29**). Prepared and isolated as a colorless oil, a 2:3:3:2 mixture of acids **18c–21c**; $^1$H-n.m.r.: $\delta$ 1.30 (d, 3 H, $J$ 6.2 Hz), 1.55 (s, 3 H), 3.51 (s, 3 H), 3.99 (dq, 1 H, $J$ 7.8, 6.2 Hz), 4.13 (d, 1 H, $J$ 7.8 Hz), 4.52 (d, 1 H, $J$ 11.3 Hz), 4.62 (d, 1 H, $J$ 11.3 Hz), and 7.33 (m, 5 H); $^{13}$C-n.m.r.: $\delta$ 15.9, 17.3, 53.2, 71.2, 71.7, 84.5, 87.0, 126.9, 127.6, 128.3, 135.2, and 172.0; $m/z$ calc. for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1203.

(*1'S,3S,4R*)-*4-[1'-(benzyloxy)ethyl]-3-methoxy-3-methyloxetan-2-one* (**30**). — Prepared and isolated as a colorless oil; $^1$H-n.m.r.: $\delta$ 1.20 (d, 3 H, $J$ 6.2 Hz), 1.59 (s, 3 H), 3.50 (s, 3 H), 3.90 (dq, 1 H, $J$ 8.2, 6.2 Hz), 4.17 (d, 1 H, $J$ 8.2 Hz), 4.62 (d, 1 H, $J$ 11.8 Hz), 4.69 (d, 1 H, $J$ 11.8 Hz), and 7.34 (m, 5 H), $^{13}$C-n.m.r.: $\delta$ 15.6, 17.1, 53.1, 71.5, 73.2, 86.2, 86.6, 127.3, 127.5, 128.1, 138.2, and 170.1; $m/z$ calc. for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1210.

*Saponification of β-lactone* **26**. — A mixture of 57.5 mg (0.23 mmol) of β-lactone **26** and 15 mg (0.11 mmol) of powdered $K_2CO_3$ was heated under vacuum, for 1 h at 100°, during which time the mixture became brown. The solid material was taken up in 20 mL of water, and extracted with 10 mL of ethyl ether. The aq. fraction was acidified to pH 3 (as judged from pHydrion paper), and extracted with three 15-mL portions of $CH_2Cl_2$. The combined $CH_2Cl_2$ fractions were dried over $Na_2SO_4$, and the solvent was removed to give 46 mg (75%) of β-hydroxy acid **19c** as a colorless oil.

*(3R, 4S, 5S)- and (3R,4S, 5S)-3,5-Dimethyl-3-methoxytetrahydrofuran-2-on-4-yl benzoate* (**33** *and* **34**). — To a solution of 282 mg (1.00 mmol) af a 3:1 mixture of β-hydroxy esters **18a** and **19a** in 25 mL of MeOH was added 30 mg of 5% Pd–C and 0.30 mL of conc. HCl. The mixture was stirred under $H_2$ for 16 h and diluted with 50 mL of ether. The mixture was filtered through a Celite pad, and extracted with 25 mL of water. The aqueous fraction was extracted with 25 mL of ether and the combined organic fractions were washed with 25 mL of brine, dried over $MgSO_4$, and evaporated. The resulting hydroxy lactones **31** and **32** (144 mg, 90%) were acylated without further purification; $\nu_{max}^{CHCl_3}$ 3540 and 1760 $cm^{-1}$, $^1$H-n.m.r.: δ 1.42 (s, 3 H), 1.42 (d, 3 H, *J* 7 Hz), 2.95 (br s, 1 H), 3.41 (s, 3 H), 4.13 (m, 1 H), and 4.26 (dq, 1 H, *J* 8, 7 Hz).

To a stirring solution of 140 mg (0.87 mmol) of the foregoing hydroxylactones in 15 mL of ether, at 0°, was added 0.153 mL (1.10 mmol) of $Et_3N$, 0.116 mL (1.00 mmol) of BzCl, and 0.020 g (0.16 mmol) of 4-(dimethylamino)pyridine. The mixture was stirred 24 h, during which time the ice bath gradually expired. The reaction mixture was partitioned between 15 mL of water and 25 mL of ether. The aq. layer was washed with two 25-mL portions of ether. The combined organic fractions were extracted with 15 mL of brine, dried over $MgSO_4$, and the solvents were removed to obtain 200 mg (80%) of ester lactones **33** and **34** as a yellow oil; $\nu_{max}$ 1765 and 1720 $cm^{-1}$. The residue was purified by silica gel column chromatography using 1:19 ether–hexane as eluant to obtain the purified lactones.

*Compound* **33** had $^1$H-n.m.r: δ 1.50 (d, 3 H, *J* 6.4 Hz), 1.54 (s, 3 H), 3.40 (s, 3 H), 4.74 (dq, 1 H, *J* = 7.4, 6.4 Hz), 5.10 (d, 1 H, *J* 7.6 Hz), 7.48 (m, 2 H), 7.51 (m, 1 H), 8.10 (m, 1 H); $^{13}$C-n.m.r.: δ 17.4, 17.9, 52.3, 75.9, 77.9, 79.3, 165.4, and 171.8.

*Anal.* Calc. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.80; H, 6.03.

*Compound* **34** had $^1$H-n.m.r.: δ 1.52 (s, 3 H), 1.59 (d, 3 H, *J* 6.5 Hz), 3.44 (s, 3 H), 4.49 (dq, 1 H, *J* 6.5, 4.3 Hz), 5.37 (d, 1 H, *J* 4.3 Hz), 7.5 (m, 3 H), and 8.1 (m, 2 H); $^{13}$C-n.m.r.: δ 17.4, 18.8, 51.7, 78.0, 80.0, 164.0, and 173.1; m/z calc. for $C_{14}H_{17}O_5$: 265.1076. Found: 265.1081.

*Protection of β-hydroxy esters* **18a**–**20a**: — To a stirring solution of 28.6 g (77.0 mmol) of a 70:23:7 mixture of β-hydroxy esters **18a**, **19a**, and **20a** and 29.2 mL (22.0 g, 170 mmol) of diisopropylethylamine in 250 mL of $CH_2Cl_2$ at 0° was added 21.6 mL (24.3 g, 155 mmol) of chloromethyl benzyl ether. The mixture was stirred for 16 h, during which time the ice bath slowly expired. The solvents were removed and the residue was partitioned between 500 mL of pentane and 75 mL of cold 5% aq. HCl solution. The organic layer was washed with three 75-mL portions of cold 5% HCl, 75 mL of saturated aq. $NaHCO_3$, 75 mL of brine, and dried over $Na_2SO_4$. The solvent was

removed and the residue was purified by flash chromatography using 250 g of silica gel and 1:4 ether–hexanes as eluant to obtain 32.0 (103%) of the mixture of **35**, **36**, and **37** ($R_F$ 0.3) as a colorless oil in the same 70:23:7 ratio of diastereomers as judged from the $^1$H-n.m.r. spectrum. This material was used without further purification. Analytical data was obtained on a racemic mixture of compounds **35–37**. The mixture has been further purified by preparative l.c. using 1:19 ether–hexane as the eluant to obtain pure **36** and an inseparable mixture of ethers **35** and **37** in 9:1 ratio as determined by the $^1$H-n.m.r. spectrum; $\nu_{max}$ 1745 and 1128 cm$^{-1}$.

*Anal.* Calc. for $C_{23}H_{30}O_6$: C, 68.67; H, 7.51. Found: C, 68.56; H, 7.39.

*Methyl-4-*O*-benzyl-3-*O*-(benzyloxymethyl)-5-deoxy-2-*C*-methyl-2-*O*-methyl-*L*-ribonate* (**35**): — $^1$H-n.m.r.: $\delta$ 1.29 (d, 3 H, *J* 6.3 Hz), 1.51 (s, 3 H), 3.40 (s, 3 H), 3.49 (s, 3 H), 3.80 (dq, 1 H, *J* 4.8, 6.3 Hz), 4.05 (d, 1 H, *J* 4.8 Hz), 4.46 (s, 2 H), 4.67 (dd, 2 H, *J* 11.0, 21.3 Hz), 4.93 (dd, 2 H, *J* 6.8, 24.2 Hz), and 7.33 (m, 10 H); $^{13}$C-n.m.r.: $\delta$ 16.1, 17.6, 51.4, 51.9, 70.1, 70.3, 74.3, 80.7, 84.1, 96.1, 127.3, 127.8, 128.0, 137. 5, 138.3, and 172.9.

*Methyl 4-*O*-benzyl-3-*O*-(benzyloxymethyl)-5-deoxy-2-*C*-methyl-2-*O*-methyl-*L*-arabinonate* (**36**) — $^1$H-n.mr.: $\delta$ 1.32 (d, 3 H, *J* 6.1 Hz), 1.39 (s, 3 H), 3.23 (s, 3 H), 3.49 (s, 3 H). 3.62 (dq, 1 H, *J* 6.6, 6.1 Hz), 4.03 (d, 1 H, *J* 6.6 Hz), 4.44 (dd, 2 H, *J* 11.4, 31.5 Hz), 4.61 (dd, 2 H, *J* 12.0, 13.9 Hz), 4.94 (s, 2 H), and 7.31 (m, 10 H).

*Methyl 4-*O*-benzyl-3-*O*-(benzyloxymethyl)-5-deoxy-2-*C*-methyl-2-*O*-methyl-4-*O*-*L*-lyxonate* (**37**). — $^1$H-n.m.r.: $\delta$ 1.25 (d, 3 H, *J* 6.1 Hz), 1.45 (s, 3 H), 3.37 (s, 3 H), 3.50 (s, 3 H), 3.78 (dq, 1 H, *J* 4.8, 6.1 Hz), 4.01 (d, 1 H, *J* 4.8 Hz), 4.46 (s, 2 H), 4.61 (dd, 2 H, *J* 16.0, 18.1 Hz), 4.85 (dd, 2 H, *J* 6.6, 13.2 Hz), and 7.33 (m, 10 H).

*$LiAlH_4$ reduction of esters* **35–37**. — The general procedure for reduction of aldols was followed with 1.72 g (43.0 mmol) of $LiAlH_4$ in 500 mL of ether and 17.3 g (43.0 mmol) of the esters **35**, **36**, **37** (70:23:7 ratio). The mixture was kept for 2 h at 0°, and then quenched in the normal manner (Fieser workup [18]) to obtain 27.0 g of a crude product that was subjected to column chromatography using 1:4 ethyl acetate–hexane as eluant to obtain 5.38 g (14.2 mmol, 33% yield) of **38a** in 98% diastereomeric purity as judged from the $^1$H-n.m.r. spectrum, and 10.1 g (27.0 mmol, 62% yield) of a mixture of the alcohols **38a**, **38b**, **38c** (57:28:14) as a colorless oil. This mixture could be separated into its components by preparative l.c. using 1:9 EtOAc–hexane as the eluant. When the purified ester **35** was reduced, the alcohol **38a** was isolated in 99% yield as a colorless oil. Analytical data was obtained on a racemic mixture of diastereomers; $\nu_{max}$ 3470 and 1605 cm$^{-1}$.

*Anal.* Calc. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08 Found: C, 70.70; H, 7.95.

*2-*O*-Benzyl-3-*O*-(benzyloxymethyl)-1-deoxy-4-*C*-methyl-4-*O*-methyl-*D*-ribitol* (**38a**). — $^1$H-n.m.r.: $\delta$ 1.05 (s, 3 H), 1.26 (d, 2 H, *J* 6.4 Hz), 2.94 (dd, 1 H, *J* 6.5, 7.4 Hz), 3.29 (s, 3 H), 3.56 (dd, 1 H, *J* 7.4, 12.0 Hz), 3.66 (dd, 1 H, *J* 6.5, 12.3 Hz), 3.91 (dq, 1 H, *J* 1.2, 6.4 Hz), 4.12 (d, 1 H, *J* 1.2 Hz), 4.54 (s, 2 H), 4.68 (dd, 2 H, *J* 11.9, 27.1 Hz), 4.88 (d, 1 H, *J* 6.1 Hz), 5.03 (d, 1 H, *J* 6.1 Hz), and 7.34 (m, 10 H).

*2-*O*-Benzyl-3-*O*-(benzyloxymethyl)-1-deoxy-4-*C*-methyl-4-*O*-methyl-*D*-arabinitol* (**38b**). — $^1$H-n.m.r.: $\delta$ 1.20 (s, 3 H), 1.32 (d, 3 H, *J* 6.3 Hz), 3.07 (dd, 1 H, *J* 7.0, 7.0 Hz), 3.26 (s, 3 H), 3.44 (dd, 1 H, *J* 6.9, 11.7 Hz), 3.75 (dd, 1 H, *J* 7.0, 11.6 Hz), 3.86 (dq, 1 H, *J*

2.6, 6.3 Hz), 3.94 (d, 1 H, *J* 2.6 Hz), 4.46 (d, 1 H, *J* 11.7 Hz), 4.57 (d, 1 H, *J* 11.7 Hz), 4.62 (d, 1 H, *J* 11.9 Hz), 4.75 (d, 1 H, *J* 11.9 Hz), 4.90 (d, 1 H, *J* 6.5 Hz), 5.01 (d, 1 H, *J* 6.5 Hz), and 7.33 (m, 10 H).

*2-O-Benzyl-3-O-(benzyloxymethyl)-1-deoxy-4-C-methyl-4-O-methyl-D-lyxitol* (**38c**). — $^1$H-n.m.r.: $\delta$ 1.09 (s, 3 H), 1.33 (d, 3 H, *J* 4.4 Hz), 3.00 (dd, 1 H, *J* 6.9, 6.9 Hz), 3.24 (s, 3 H), 3.50 (dd, 1 H, *J* 6.9, 12.1 Hz), 3.68 (dd, 1 H, *J* 6.9, 12.1 Hz), 3.83 (dq, *J* 2.6, 4.4 Hz), 3.91 (d, 1 H, *J* 2.6 Hz), 4.46 (d, 1 H, *J* 11.5 Hz), 4.59 (d, 1 H, *J* 11.8 Hz), 4.88 (dd, 2 H, *J* 6.8, 18.6 Hz), 4.96 (s, 2 H), and 7.33 (m, 10 H).

*4-O-Benzyl-3-O-(benzyloxymethyl)-5-deoxy-2-C-methyl-2-O-methyl-L-ribose* (**39**). — To a stirring solution of 0.45 mL (0.66 g, 5.21 mmol) of oxalyl chloride in 10 mL of $CH_2Cl_2$, at $-65°$, was added a solution of 0.74 mL (0.81 g, 10.4 mmol) of $Me_2SO$ in 2.0 mL of $CH_2Cl_2$. After 5 min at 65° 1.50 g (4.01 mmol) of a solution of alcohol **38a** in 4.0 mL of $CH_2Cl_2$ was added. The mixture was stirred for 25 min at $-65°$, and 3.35 mL (2.44 g, 24.1 mmol) of $Et_3N$ was added. The white suspension was allowed to warm to room temperature, diluted with $CH_2Cl_2$, and washed with water and brine. The organic fraction was dried over $Na_2SO_4$ and the solvent was removed. The residue was taken up in 75 mL of hexane and washed with two portions of 1% aq. HCl and brine. The organic fraction was dried over $Na_2SO_4$, and the solvent was removed to obtain 1.43 g (96%) of aldehyde **39** as a yellow oil; $\nu_{max}$ 1735 and 1460 cm$^{-1}$; $^1$H-n.m.r.: $\delta$ 1.26 (d, 3 H, *J* 5.8 Hz), 1.34 (s, 3 H), 3.39 (s, 3 H), 3.78 (m, 2 H), 4.48 (d, 1 H, *J* 11.6 Hz), 4.52 (d, 1 H, *J* 11.6), 4.61 (d, 1 H, *J* 11.9 Hz), 4.68 (d, 1 H, *J* 11.9 Hz), 4.83 (d, 1 H, *J* 7.8 Hz), 4.91 (d, 1 H, *J* 7.8 Hz), 7.35 (m, 10 H), and 9.45 (s, 1 H); $^{13}$C-n.m.r.: $\delta$ 14.9, 16.3 52.1, 70.4, 70.8, 74.1, 83.1, 85.7, 96.7, 127.4, 127.5, 127.7, 128.2, 128.3, 137.5, 138.0, and 202.0.

*Anal.* Calc. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.77; H, 7.36.

*(3R,4S,5S)-5-Benzyl-4-(benzyloxy)methoxy-3-methoxy-3-methyl-hex-1-ene* (**40**). — To a stirring solution of 2.69 g (7.52 mmol) of methyltriphenylphosphonium bromide in 15 mL of THF, at 0°, was added 5.01 mL (7.52 mmol) of BuLi (1.50M in hexane), followed by a solution of 1.00g (2.69 mmol) of aldehyde **39** in 2 mL of THF. The syringe that delivered aldehyde **39** was rinsed with 1.0 mL of THF. The mixture was stirred for 90 min at 0° and partitioned between 250 mL of ether and 75 mL of water. The organic fraction was washed with two 75-mL portions of water and brine. The organic fraction was dried over $K_2CO_3$, and the solvents were removed. The residue was purified by silica gel column chromatography using 1:19 ether–hexane as eluant to afford 0.958 g (96%) of alkene **40** as a colorless oil; $[\alpha]_D^{23}$ + 12.53 (C = 0.0071, $CHCl_3$); $\nu_{max}$ 1455 and 1033 cm$^{-1}$; $^1$H-n.m.r.:$\delta$ 1.28 (d, 3 H, *J* 6.4 Hz). 1.32 (s, 3 H), 3.16 (s, 3 H), 3.85 (m, 2 H), 4.47 (d, 1 H, *J* 11 Hz), 4.49 (d, 1 H, *J* 11 Hz), 4.62 (d, 1 H, *J* 11.9 Hz), 4.75 (d, 1 H, *J* 11.9 Hz), 4.88 (d, 1 H, *J* 6.7 Hz), 5.05 (d, 1 H, *J* 6.7 Hz), 5.22 (d, 1 H, *J* 16.6 Hz), 5.34 (d, 1 H, *J* 11.0 Hz), 5.83 (dd, 1 H, *J* 11.0, 16.6 Hz), and 7.35 (m, 10 H).

*Anal.* Calc. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.77; H, 8.20.

*5-O-Benzyl-4-O(benzyloxymethyl)-2,6-dideoxy-3-C-methyl-3-O-methyl-L-ribo-hexitol* (**41**). — To a stirring solution of 958 mg (2.59 mmol) of alkene **40** in 1.5 mL of THF, at 25°, was added a solution of 694 mg (5.69 mmol) of 9-borabicyclonane in 12 mL of THF. The mixture was stired for 16 h, placed in a 0° ice–water wath, and treated with

2.15 mL of 30% $H_2O_2$ in 3.25 mL of EtOH and 1.10 mL of water. The mixture was stirred for 1 h at 0° and partitioned between 125 mL of ether and 30 mL of water. The organic fraction was dried over $MgSO_4$ and the solvents were removed. The residue was purified by silica gel column chromatography using 3:7 EtOAc–hexane as the eluant to afford 842 mg (84%) of alcohol **41** as a colorless oil; $\nu_{max}$ 3480 and 1458 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.21 (s, 3 H), 1.27 (d, 3 H, *J* 6.3 Hz), 1.69 (m, 1 H), 2.02 (m, 1 H), 2.77 (dd, 1 H, *J* 4.7, 6.2 Hz), 3.23 (s, 3 H), 3.80 (m, 3 H), 3.93 (d, 1 H, *J* 1.9 Hz), 4.46 (d, 1 H, *J* 11.8 Hz), 4.55 (d, 1 H, *J* 11.8 Hz), 4.62 (d, 1 H, *J* 12.0 Hz), 4.74 (d, 1 H, *J* 12.0 Hz), 4.88 (d, 1 H, *J* 4.6 Hz), 5.02 (d, 1 H, *J* 4.6 Hz), and 7.35 (m, 10 H).

*Anal.* Calc. for $C_{23}H_{32}O_5$: C, 71.11, H, 8.30. Found: C, 70.79; H, 8.29.

*5-O-Benzyl-4-O-(benzyloxymethyl)-2,6-dideoxy-3-C-methyl-3-O-methyl*-L-ribo-*hexose* (**42**). — To a stirring solution of 0.25 mL (360 mg, 2.82 mmol) of oxalyl chloride in 5 mL of $CH_2Cl_2$, at −65° was added a solution of 0.40 mL (440 mg, 5.63 mmol) of $Me_2SO$ in 1 mL of $CH_2Cl_2$. The syringe that delivered the $Me_2SO$ was rinsed with 1.0 mL of $CH_2Cl_2$. This solution was stirred for 10 min at −65°, and 0.842 g (2.17 mmol) of the alcohol **41** in 2 mL of $CH_2Cl_2$ was added. The syringe that delivered the alcohol was rinsed with 1.0 mL of $CH_2Cl_2$. After 15 min at −70° 1.88 ml (1.31 g, 13.0 mmol) of $Et_3N$ was added. The white suspension was warmed to room temperature, diluted with $CH_2Cl_2$, and washed with water and brine. The organic fraction was dried over $Na_2SO_4$ and the solvent was removed. The residue was taken up in 50 mL of pentane and washed with water and brine. The organic fraction was dried over $Na_2SO_4$, and the solvent was removed to obtain 704 mg (1.82 mmol, 84%) of aldehyde **42** as a colorless oil; $\nu_{max}$ 1720 and 1460 $cm^{-1}$; $^1$H-n.m.r.: $\delta$ 1.26 (s, 3 H), 1.27 (d, 3 H, *J* 6.2 Hz), 2.47 (dd, 1 H, *J* 3.1, 15.4 Hz), 2.72 (dd, 1 H, *J* 2.8, 15.4 Hz), 3.25 (s, 3 H), 3.81 (dq, 1 H, *J* 2.1, 6.4 Hz), 4.00 (d, 1 H, *J* 2.1 Hz), 4.46 (d, 1 H, *J* 11.8 Hz), 4.55 (d, 1, *J* 11.8 Hz), 4.60 (d, 1 H, *J* 12.0 Hz), 4.68 (d, 1 H, *J* 12.0 Hz), 4.86 (d, 1 H, *J* 6.3 Hz), 4.98 (d, 1 H, *J* 6.3 Hz), 7.35 (m, 10 H), and 9.82 (dd, 1 H, *J* 2.9, 2.9 Hz).

*Anal.* Calc. for $C_{23}H_{28}O_5$: C, 71.48; H, 7.82. Found: C, 71.26; H, 7.66.

*2,6-Dideoxy-3-C-methyl-3-O-methyl-α*-L-ribo-*hexopyranose and 2,6-dideoxy-3-C-methyl-3-O-methyl-β*-L-ribo-*hexopyranose* (*α-L-cladinose and β-L-cladinose*, **1α** *and* **1β**). — A mixture of 704 mg (1.82 mmol) of aldehyde **42**, 30 mg of 10% Pd–C, and 0.25 mL of 0.7mM $HClO_4$ in 3 ml of EtOAc was stirred under hydrogen. The transient formation of hemiacetal **43** and benzyl alcohol were indicated by t.l.c. analysis using 3:7 EtOAc–hexane as eluant. To the stirring mixture was added another 100 mg of Pd–C and 1.0 mL of 0.7 mM $HClO_4$ in EtOAc. The immediate uptake of two equivalents of $H_2$ gas was indicated. The mixture was stirred for 2 h, diluted with EtoAc, and the catalyst was removed by suction filtration through a Celite pad. To the stirring solution was added 1.0 g of $K_2CO_3$. The mixture was filtered through a Celite pad, and the solvent was removed. The residue was purified by silica gel column chromatography using 3:7 EtOAc–hexane as the eluant to obtain 256 mg (80%) of L-cladinose as a light-yellow oil as a 19:81 ratio of *α* and *β* anomers (**1α** and **1β**) as judged from the $^1$H-n.m.r. spectrum. The i.r. and $^1$H-n.m.r. spectra were identical with a sample prepared[15] by acid hydrolysis of erythromycin A; $\nu_{max}$ 3660, 3430, and 1070 $cm^{-1}$.

*Anomer* **1α** — $^1$H-n.m.r.: $\delta$ 1.31 (s, 3 H), 1.32 (d, 3 H, $J$ 6.2 Hz), 1.60 (dd, 1 H, $J$ 3.7, 14.8 Hz), 2.05 (d, 1 H, $J$ 10.9 Hz), 2.24 (dd, 1 H, $J$ 1.4, 4.8 Hz), 3.05 (d, 1 H, $J$ 9.7 Hz), 3.37 (s, 3 H), 3.92 (dq, 1 H, $J$ 9.7, 6.2 Hz), and 5.07 (dd, 1 H, $J$ 3.7, 11.7 Hz); $^{13}$C-n.m.r.: $\delta$ 14.8, 20.8, 36.2, 49.9, 70.6, 75.4, 77.6, and 91.9.

*Anomer* **1β** — $^1$H-n.m.r.: $\delta$ 1.26 (s, 3 H), 1.30 (d, 3 H, $J$ 6.2 Hz), 1.37 (dd, 1 H, $J$ 13.7, 9.6 Hz), 2.10 (d, 1 H, $J$ 11.2 Hz), 2.29 (dd, 1 H, $J$ 20, 4.3 Hz), 2.98 (dd, 1 H, $J$ 10.0, 9.5 Hz), 3.26 (s, 3 H), 3.66 (dq, 1 H, $J$ 9.5, 6.1 Hz), 4.91 (ddd, 1 H, $J$ 1.8, 9.6, 19.0 Hz); $^{13}$C-n.m.r.: $\delta$ 17.8, 20.6, 38.7, 48.6, 70.4, 77.5, and 91.6.

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