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Synthesis of 1-Deoxy-D-galactohomonojirimycin via Enantiomerically Pure Allenylstannanes

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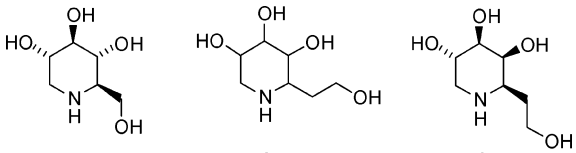
1-Deoxy-D-galactohomonojirimycin was synthesized in seven steps from optically pure allenylstannane **4** and L-lactate-derived aldehyde **5** in 48% overall yield. The key step was the Lewis acid catalyzed reaction of **4** and **5** to give the *syn*-amino alcohol in excellent yield and very high diastereoselectivity.

Introduction

Polyhydroxylated piperidine alkaloids (azasugars) have been the subject of intensive investigation because of their ability to inhibit carbohydrate-processing enzymes.[1,2] The wide range of biological activities displayed by this class of compounds has resulted in extensive synthetic studies.[3] 1-Deoxyazasugars are of particular interest because of their enhanced stability.[4] Among these, 1-deoxynojirimycin[5] (**1**) and its stereoisomers[6] have been the target of a number of recent syntheses, as have their C-6 homologues **2**.[7] Recently, an efficient synthesis of optically active α-aminoallenylstannanes[8] as well as



1 **2** **3**

their highly syn selective reactions with aldehydes was reported from these laboratories.[9] The application of this methodology to the synthesis of 1-deoxy-D-galactohomonojirimycin (**3**)[10] is reported below.

Results and Discussion

The synthesis of 1-deoxy-D-galactohomonojirimycin (**3**) is presented in Scheme 1. Optically active allenylstannane **4** was synthesized as previously described[9] from propargyl bromide and optically active diphenyloxazolidinone in 54% overall yield. The requisite aldehyde **5** was synthesized by protection of diethyl L-tartrate as the

(1) For a review on the mechanism of enzymic glycosyl transfer, see: Sinot, M. L. *Chem. Rev.* **1990**, *90*, 1171.

(2) For reviews on azasugar inhibitors, see: (a) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1. (b) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (c) Sears, P.; Wong, C. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (d) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999.

(3) For recent reviews, see: (a) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223. (b) Asano, N.; Hashimoto, H. *Glycosciences* **2001**, *3*, 2541. (c) Kazmaier, U. *Recent Res. Dev. Org. Chem.* **1998**, *2* (part 2), 351.

(4) For recent synthetic efforts, see the following and the references therein: (a) Han, H. *Tetrahedron Lett.* **2003**, *44*, 157. (b) Sawada, D.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2003**, *44*, 3085. For reviews, see: (c) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959. (d) Zhow, W.-S.; Lu, Z.-H.; Xu, Y.-M.; Liao, L.-X.; Wang, Z.-M. *Tetrahedron* **1999**, *55*, 11959.

(5) (a) Somfai, P.; Marchand, P.; Torsell, S.; Lindström, U. M. *Tetrahedron* **2003**, *59*, 1293. (b) Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839. (c) Kiguchi, T.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 5819. (d) Matos, C. R. R.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **1999**, 571. (e) Kazmaier, U.; Grandel, R. *Eur. J. Org. Chem.* **1998**, 1833. (f) Lindström, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173.

(6) (a) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281. (b) Spreitz, J.; Stutz, A. E.; Wrodnigg, T. M. *Carbohydr. Res.* **2002**, *337*, 183. (c) Mehta, G.; Mahal, N. *Tetrahedron Lett.* **2000**, *41*, 5741. (d) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *10*, 8931. (e) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741.

(7) (a) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065. (b) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, *57*, 39. (c) Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2579. (d) Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. *Chem. Commun.* **2000**, 471. (e) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *Chem. Commun.* **1999**, 1719. (f) Compernolle, F.; Joly, G.; Peetars, K.; Toppet, S.; Hoonaert, G. *Tetrahedron* **1997**, *53*, 12739. (g) Herders, C.; Schiffer, T. *Tetrahedron* **1996**, *52*, 14745. (h) Lundt, I.; Madsen, R. *Synthesis* **1995**, 787. (i) Kilonda, A.; Compernolle, F.; Toppet, S.; Hoornaert, G. J. *Tetrahedron Lett.* **1994**, *48*, 9047. (j) Rassu, G.; Pinna, L.; Spanu, P.; Culeddy, N.; Casiraghi, G.; Fava, G. G.; Ferrari, M. B.; Pelosi, G. *Tetrahedron* **1992**, *48*, 727.

(8) For a review on the use of chiral allenylstannanes in synthesis, see: Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.

(9) Ranslow, P. B. D.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem.* **2003**, in press.

(10) To the best of our knowledge, this particular diastereoisomer has not previously been synthesized.

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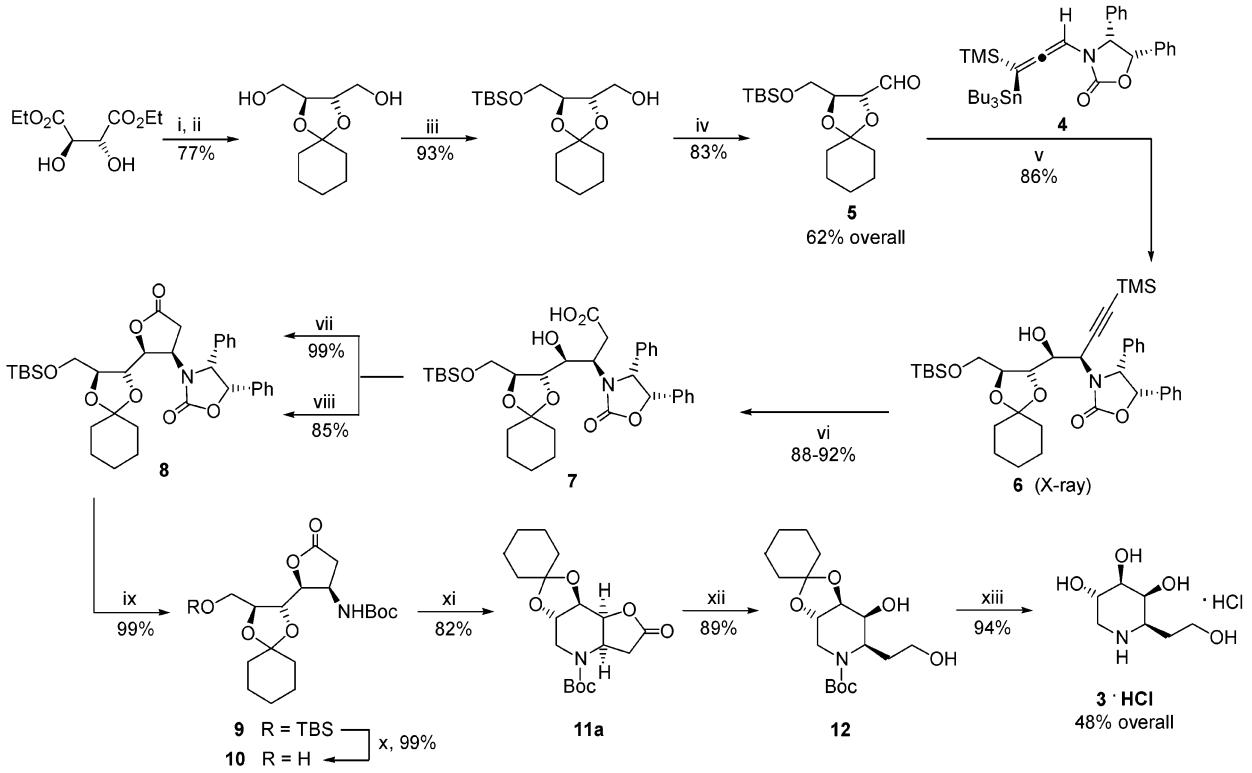
SCHEME 1[a]



[a] Reagents and conditions: (i) cyclohexanone, PhH, TsOH, rfx; (ii) $LiAlH_4$, THF, rfx; (iii) NaH, TBSCl, THF, 25 °C; (iv) Dess−Martin periodanane, CH_2Cl_2, 25 °C; (v) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −70 °C; (vi) Cy_2BH, THF, 0 → 25 °C, and then H_2O_2, aq $NaHCO_3$, 0 → 25 °C; (vii) Mukaiyama reagent, Et_3N, CH_2Cl_2, 25 °C; (viii) DEAD, Ph_3P, THF, −20 → +25 °C; (ix) 80 psi H_2, catalyst $Pd(OH)_2$, Boc_2O, THF, 25 °C; (x) HF·Py, MeCN, 25 °C; (xi) DEAD, Ph_3P, THF, −20 → +25 °C; (xii) $LiAlH_4$, THF, −20 °C; (xiii) HCl/MeOH, 25 °C.

cyclohexanone ketal followed by lithium aluminum hydride reduction to the C_2-symmetric diol. Monosilylation[11] followed by Dess−Martin oxidation produced the desired aldehyde in 62% overall yield from diethyl L-tartrate. Condensation of the aldehyde with optically active allenylstannane **4** in the presence of $BF_3{\cdot}OEt_2$ produced protected aminotetraol **6** in 86% yield with greater than 95% syn selectivity (as expected from previous studies).[9] The absolute configuration was confirmed by X-ray crystallography. Hydroboration/oxidation of the silylalkyne[12] produced hydroxy acid **7** in excellent yield.

Although 4-hydroxybutyric acids often lactonize spontaneously, hydroxy acid **7** proved resistant to cyclization, requiring activation of either the carboxylic acid (Mukaiyama)[13] or the hydroxyl group (Mitsunobu)[14] to effect lactonization. Remarkably, both procedures gave the same lactone diastereoisomer **8**, in excellent yield. This is likely to be a case of the unusual but precedented[15] Mitsunobu reaction with sterically hindered alcohols with retention.[16] Cleavage of the oxazolidinone by hydrogenolysis using Pearlman's catalyst in the presence of Boc anhydride proceeded under mild conditions and in excellent yield. Removal of the silyl protecting group was problematic. The most effective agent was HF·Py, but the process had to be closely monitored to prevent overreaction. Best yields were obtained by running the reaction to a 92% conversion. Pushing to 100% conversion decreased the yield, and the product was easily separated from the starting material. Mitsunobu cyclization of the primary alcohol **10** produced bicyclic amino lactone **11**, the stereochemistry of which was confirmed by hydrolysis of a portion of the cyclohexanone ketal (dil HCl/MeOH) and acquisition of an X-ray crystal structure of the resulting diol. Reduction of the lactone with lithium aluminum hydride followed by hydrolysis of the ketal and recrystallization from methanol/ether gave the hydrochloride salt of **3** in 48% overall yield.

A more direct route was originally planned (Scheme 2) which, although ultimately unsuccessful, revealed some interesting chemistry. Benzyl-protected aminotetraol **13** was synthesized in comparable yield following procedures developed in Scheme 1. Direct conversion of this alkyne to lactone **14** was achieved using a palladium-catalyzed process developed by Gore et al.[17] Although the transformation was successful, yields exceeding 50% could never be achieved, even when stoichiometric

(11) (a) Chattopadhyay, A.; Dhotare, B. *Tetrahedron: Asymmetry* **1998**, *9*, 2715. (b) Vriesma, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110.

(12) Alemany, C.; Bach, J.; Farras, J.; Garcia, J. *Org. Lett.* **1999**, *1*, 1831.

(13) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

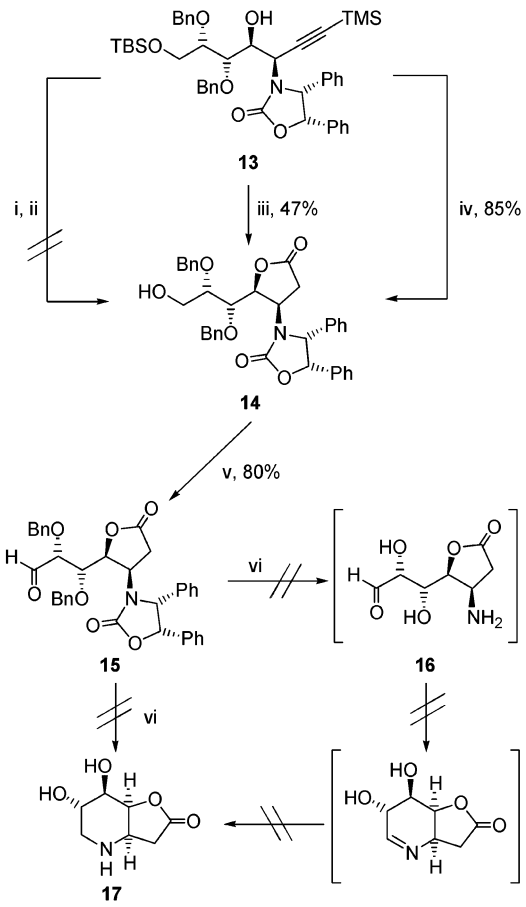
(14) (a) Mistunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(15) (a) Liao, X.; Wu, Y.; DeBrabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648. (b) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (c) Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754.

(16) Silyl migration from the terminal to the internal OH group in **6**, followed by cyclization to give an eight-membered lactone, which rearranged to the butyrolactone on subsequent desilylation, was deemed less likely.

(17) Compain, P.; Gore, J.; Vatele, J.-M. *Tetrahedron* **1996**, *52*, 10405.

SCHEME 2[a]



[a] Reagents and conditions: (i) KF, MeOH, rfx; (ii) $Cr(CO)_5$-(THF) or $Mo(CO)_5$(THF), THF, 25 °C; (iii) catalyst $Pd(OAc)_2$, catalyst $CuCl_2$, wet DMF, air, 25 °C; (iv) Scheme 1; (v) Dess–Martin periodanane, CH_2Cl_2, 25 °C; (vi) H_2, catalyst Pd/C, catalyst CSA.

amounts of palladium(II) were used. The chromium and molybdenum carbonyl catalyzed cyclization of homopropargyl alcohols of McDonald was also attempted.[18] In this case, no reaction was observed under a variety of conditions. Thus, the hydroboration/oxidation sequence in Scheme 1 provided the most efficient route from **13** to **14**.

Dess–Martin oxidation of the primary alcohol to the aldehyde went well, providing **15** in excellent yield. The protecting groups in **15** were chosen to be removed under conditions suitable for the reductive amination of aldehydes, with the hope that the free amino aldehyde **16** (Scheme 2) would spontaneously cyclize to the imine and reduce to the desired bicyclic lactone. This would shorten the synthesis by three steps. However, the hydrogenation was very sluggish and resulted in a mixture of products, none of which contained the piperidine ring. Thus, this route was abandoned.

In conclusion, an efficient synthesis of 1-deoxy-D-galactohomonojirimycin has been achieved in 48% overall yield from the literature starting materials. The synthesis is based on newly developed allenylstannane chemistry recently reported from these laboratories. An unusual Mitsunobu lactonization with *retention* prevented the use of the route for the synthesis of the D-gulodiastereoisomer of 1-deoxyhomonojirimycin.

(18) McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103 and references therein.

Experimental Section

Monosilylation of the C_2-Symmetric Diol To Produce the Tris-O-Protected Tetrol. A 60% NaH dispersion in mineral oil (1.09 g, 27 mmol) was placed in an argon-flushed 0.20 L flask and washed with dry hexanes. The oil-free hydride was suspended in dry THF (10 mL), and the reaction vessel was placed in a dry ice/acetone bath. A solution of the bis-O-protected tetrol (5.2 g, 25.5 mmol) in THF (40 mL) was added under argon with stirring. A moderate gas evolution was observed, and the reaction mixture turned into a thick slurry. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature with vigorous stirring. For a brief period of time, the reaction mixture became much less viscous and then almost completely solidified. This was diluted with dry THF (60 mL), and the resulting slurry was stirred at room temperature for 1 h. A solution of *tert*-butyldimethylchlorosilane (3.84 g, 25.5 mmol) in dry THF (20 mL) was slowly added. A moderately exothermic reaction took place, and within 5 min the reaction mixture became homogeneous. The resulting cloudy mixture was stirred further at room temperature for 2.5 h, then poured onto Et_2O (350 mL), washed with 10% w/w aq K_2CO_3 (20 mL) and brine, and dried over anhyd $MgSO_4$. The solvent removal produced a cloudy yellowish liquid (9 g), which was purified by distillation under reduced pressure to afford the title compound as a colorless oil (7.50 g). Yield: 93%. $[\alpha]^{22}_D$: +8.7 (*c* 3.9, $CHCl_3$) [lit.[11] $[\alpha]^{22}_D$: +3.54 (*c* 3.9, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.02–3.60 (m, 6H), 2.30 (bs, 1H), 1.60 (bs, 8H), 1.44–1.32 (m, 2H), 0.89 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 109.6, 79.8, 77.8, 63.9, 62.9, 36.7, 36.5, 25.9, 25.2, 24.0, 23.9, 18.2, −5.3. FT-IR (film): 3462, 2934, 2858, 1472, 1463, 1449, 1364, 1254, 1097, 837, 778 cm^{-1}. HRMS (FAB$^+$, *m*/*z*): calcd for $C_{16}H_{32}O_4Si$ (M^+), 316.2070; found, 316.2073. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.76; H, 10.13. Found: C, 60.56; H, 9.89.

Dess–Martin Oxidation of the L-Tartrate-Derived Alcohol To Produce the Aldehyde 5. To a stirred solution of the alcohol (4.74 g, 15.0 mmol) in dry CH_2Cl_2 (120 mL) was added Dess–Martin periodanane (8.27 g, 19.5 mmol) in one portion at room temperature. The reaction progress was monitored by TLC [hexanes/EtOAc (9:1); alcohol, R_f 0.2; aldehyde **5**, R_f 0.3]. The reaction mixture was poured into a vigorously stirred mixture of saturated aq $NaHCO_3$ (120 mL), saturated aq $Na_2S_2O_3$ (120 mL), and CH_2Cl_2 (120 mL). Once an organic layer became clear, it was separated and set aside. The aqueous layer was extracted with CH_2Cl_2 (500 mL). Combined organic solutions were dried over anhyd $MgSO_4$ and stripped in vacuo. Flash chromatography [140 g of silica, eluted with hexanes/Et_2O (8:2 → 1:1)] afforded pure **5** as a clear viscous liquid (3.9 g). Yield: 83%. $[\alpha]^{22}_D$: +5.7 (*c* 2.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.75 (s, 1H), 4.30 (dd, $J_1 = 1$ Hz, $J_2 = 6.9$ Hz, 1H), 4.11 (dt, $J_1 = 4.5$ Hz, $J_2 = 6.9$ Hz, 1H), 3.98–3.80 (m, 1H), 3.78 (d, $J = 4.5$ Hz, 1H), 1.80–1.30 (m, 10H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (bs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 200.9, 112.0, 81.7, 77.1, 63.1, 36.5, 35.8, 26.0, 25.9, 25.0, 23.9, 23.8, 18.4, −5.2, −5.3. FT-IR (film): 3443, 2934, 2857, 1736, 1472, 1463, 1449, 1364, 1254, 1144, 1098, 837 cm^{-1}. HRMS (FAB$^+$, *m*/*z*): calcd for $C_{16}H_{31}O_4Si$ ($M + H^+$), 315.1992; found, 315.1979.

Lewis Acid Catalyzed Addition of the Allenylstannane 4 to the Aldehyde 5 To Produce the Homopropargylic Alcohol 6. The allenylstannane **4** (6.38 g, 10.0 mmol) and freshly prepared aldehyde **5** (3.50 g, 11.1 mmol) were combined in a 100 mL Schlenk flask under argon. Dry CH_2Cl_2 (50 mL) was added, and the resulting orange solution was cooled to −78 °C under argon. Neat $BF_3{\cdot}Et_2O$ (5.6 mL, 44 mmol) was added dropwise over a period of 25 min (the first few drops

caused the solution to turn dark greenish and then dark orange). The reaction mixture was stirred between −75 and −70 °C for 48 h and then quickly poured into a vigorously stirred ice-cold mixture of CH_2Cl_2 (400 mL), saturated aq $NaHCO_3$ (200 mL), and water (200 mL). An additional portion of CH_2Cl_2 (100 mL) was used to rinse the Schlenk flask. The resulting heterogeneous mixture was stirred for an additional 15 min while slowly reaching room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were washed with saturated aq $NaHCO_3$ and brine and dried over anhyd $MgSO_4$. Solvent removal under reduced pressure afforded a clear orange oil (10 g). Flash chromatography [300 g of silica, eluted with hexanes/Et_2O (8:2 → 65:35)] afforded **6** as a cream-colored crystalline solid (5.0 g). Mixed fractions were chromatographed again to give an additional portion of pure **6** (0.7 g). X-ray quality crystals (long thin plates) were obtained by recrystallization from Et_2O/hexanes (slow evaporation). Yield: 86%. Mp: 113−114 °C (pentane). $[\alpha]^{22}_D$: −46.0 (*c* 1.70, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.11−7.03 (m, 6H), 6.92−6.88 (m, 4H), 5.80 (d, J = 8.0 Hz, 1H), 5.37 (d, J = 8.0 Hz, 1H), 4.81 (d, J = 4.0 Hz, 1H), 4.22 (d, J = 5.6 Hz, 1H), 4.11−4.06 (m, 4 lines, 2H), 3.97−3.89 (m, 6 lines, 2H), 3.77 (dd, J_1 = 5.2 Hz, J_2 = 10.8 Hz, 1H), 1.67−1.56 (m, 8H), 1.45−1.37 (m, 2H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), −0.08 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.6, 134.6, 134.2, 128.0, 127.9, 127.8, 126.2, 110.1, 98.5, 92.7, 81.1, 79.8, 77.7, 74.3, 65.1, 64.2, 49.7, 36.7, 36.3, 25.9, 25.1, 23.9, 23.8, 18.4, −0.44, −5.4. FT-IR (film): 3396, 2933, 2857, 2180, 1739, 1455, 1407, 1250, 843 cm^{-1}. Anal. Calcd for $C_{37}H_{53}NO_6Si_2$: C, 66.97; H, 7.99; N, 2.11. Found: C, 67.12; H, 7.91; N, 2.11.

Hydroboration/Oxidation of the Homopropargylic Alcohol 6 To Produce the γ-Hydroxycarboxylic Acid 7. To a stirred solution of cyclohexene (5.0 mL, 50 mmol) in dry THF (24 mL) was slowly added 1.0 M BH_3·THF (25 mL, 25 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature, while dicyclohexylborane started to precipitate from the solution. The stirring was continued for 1 h at room temperature. The resulting dicyclohexylborane suspension was cooled to −15 °C under argon, and a solution of **6** (3.10 g, 4.65 mmol) in dry THF (48 mL) was added dropwise with a concominant gas evolution. The resulting mixture was allowed to reach room temperature, and the stirring was continued until the reaction mixture became clear (ca. 1 day). This was placed in an ice bath, and a solution of $NaHCO_3$ (8.4 g, 0.10 mol) and 30% aq H_2O_2 (19 mL) in water (50 mL) was carefully added with efficient stirring so that the internal temperature was kept below 15 °C. Once the exothermic reaction was over, the cooling bath was removed, and the reaction mixture was stirred for an additional 3 h at room temperature. Most of the THF was removed under reduced pressure. The resulting aqueous slurry was taken-up in CH_2Cl_2, and the aqueous layer was adjusted to pH 6−7 by adding small portions of saturated aq NH_4Cl, with occasional stirring between additions. The organic layer was separated and set aside. The aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic portions (cloudy) were combined and concentrated under vacuum to approximately half the original volume and then stirred vigorously for several minutes with a saturated aqueous solution of $NaHCO_3$ (0.6 g). The resulting cloudy mixture was treated with silica, and the solvent was removed under reduced pressure. The silica, loaded with a crude mixture, was transferred onto a column (100 mg of silica, Et_2O) and eluted with Et_2O until all of the cyclohexanol came off. The γ-hydroxycarboxylic acid was eluted using a mixture of Et_2O/MeOH/AcOH (90:10:1), affording pure **7** as a colorless foam (2.57 g). Yield: 88%. Mp: 108−110 °C (AcOH). $[\alpha]^{22}_D$: −3.8 (*c* 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.13−6.92 (m, 10H), 5.84 (d, J = 8.0 Hz, 1H), 5.37 (d, J = 8.0 Hz, 1H), 4.73 (bs, 1H), 4.38 (d, J = 4.0 Hz, 1H), 4.02 (dd, J_1 = 6.0 Hz, J_2 = 10.4 Hz, 1H), 3.95−3.82 (m, 7 lines, 2H), 2.82−3.68 (m, 2H), 2.74−2.56 (ABX, 8 lines, 2H), 1.58−1.45 (m, 8H), 1.40−1.25 (m, 2H), 0.97 (s, 9H), 0.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.5, 159.2, 134.7, 134.3, 128.4, 128.3, 128.1, 127.8, 125.9, 110.2, 80.8, 80.4, 78.3, 74.3, 65.4, 64.3, 53.0, 36.5, 36.2, 34.0, 25.9, 25.0, 23.7, 23.6, 18.4, −5.4. FT-IR (film): 2933, 2857, 1733, 1718, 1457, 1418, 1362, 1252, 1116, 837 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{34}H_{48}NO_8Si$ ($M + H^+$), 626.3149; found, 626.3148. Anal. Calcd for $C_{34}H_{47}NO_8Si$: C, 65.28; H, 7.52; N, 2.24. Found: C, 65.32; H, 7.46; N, 2.36.

Lactonization of the γ-Hydroxycarboxylic Acid 7 To Produce the Lactone 8. A mixture of the γ-hydroxycarboxylic acid **7** (0.85 g, 1.36 mmol) and the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) (0.70 g, 2.7 mmol) was dissolved in dry CH_2Cl_2 (34 mL). The resulting yellow suspension was stirred and treated with Et_3N (0.76 mL, 5.4 mmol) at room temperature. Within 10 min after the addition, no starting material could be detected by TLC. The reaction mixture was poured into a mixture of Et_2O (150 mL) and CH_2Cl_2 (50 mL). The resulting yellowish opaque mixture was washed with saturated aq $NaHCO_3$ (resulting in almost complete decolorization of both layers) and brine. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). Combined organic solutions were dried over anhyd $MgSO_4$ and concentrated to produce an orange oil. Flash chromatography (45 g of silica, eluted with Et_2O) afforded **8** as an off-white foam, which was further recrystallized from CH_2Cl_2/hexanes (0.82 g). Yield: 99%. Mp: 187 °C (Et_2O). $[\alpha]^{22}_D$:+10.9 (*c* 1.95, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.16−7.06 (m, 6H), 6.99−6.80 (m, 4H), 5.89 (d, J = 7.6 Hz, 1H), 5.07 (d, J = 7.6 Hz, 1H), 5.07−4.99 (m, 1H), 4.63 (dd, J_1 = 6.0 Hz, J_2 = 9.2 Hz, 1H), 4.39 (dd, J_1 = 7.6 Hz, J_2 = 8.8 Hz, 1H), 4.18−4.13 (m, 1H), 3.97 (dd, J_1 = 2.4 Hz, J_2 = 11.6 Hz, 1H), 3.85 (dd, J_1 = 2.8 Hz, J_2 = 11.6 Hz, 1H), 2.40−2.26 (ABX, 7 lines, 2H), 1.82−1.60 (m, 8H), 1.54−1.32 (m, 2H), 0.96 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.3, 157.7, 135.0, 133.5, 128.7, 128.5, 128.0, 127.8, 125.9, 111.1, 82.0, 81.1, 80.4, 72.2, 64.7, 62.1, 51.4, 36.8, 36.6, 31.2, 26.0, 25.1, 23.9, 23.8, 18.4, −5.1, −5.3. FT-IR (film): 2932, 2856, 1792, 1762 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{34}H_{46}NO_7Si$ ($M + H^+$), 608.3044; found, 608.3057. Anal. Calcd for $C_{34}H_{45}NO_7Si$: C, 67.22; H, 7.41; N, 2.31. Found: C, 67.10; H, 7.28; N, 2.23.

Hydrogenation of the Diphenyloxazolidinone Moiety in 8 To Produce the NHBoc Lactone (9). The lactone **8** (169 mg, 0.278 mmol), Boc_2O (0.12 g, 0.55 mmol), Pearlman's catalyst (wet 20% $Pd(OH)_2$, 0.10 g, 0.14 mmol), and EtOAc (6 mL) were combined under argon in a thick-walled glass tube. The tube was fitted with a pressure head, flushed several times with hydrogen, and then pressurized to 80 psi H_2. The reaction mixture was stirred vigorously at room temperature with occasional flushing/repressurizing with H_2. Reaction progress was monitored by TLC [hexanes/Et_2O (1:1); **8**, R_f 0.1; **9**, R_f 0.3]. The catalyst was removed by passing the reaction mixture through a Celite pad followed by thorough rinsing with THF. Flash chromatography of the concentrated filtrates [9 g of silica, eluted with hexanes/Et_2O (6:4)] afforded pure **9** as a colorless crystalline solid (135 mg). Yield: 99%. Mp: 99−100 °C (Et_2O/hexanes). $[\alpha]^{22}_D$: −4.6 (*c* 2.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.87 (bs, 1H), 4.68−4.55 (m, 1H), 4.58 (q, J = 5.6 Hz, 1H), 4.25 (dd, J_1 = 5.6 Hz, J_2 = 8.0 Hz, 1H), 4.00 (qt, J = 4.4 Hz, 1H), 3.83−3.73 (ABX, 8 lines, 2H), 2.86 (dd, J_1 = 7.4 Hz, J_2 = 17.6 Hz, 1H), 2.60 (dd, J_1 = 6.0 Hz, J_2 = 17.6 Hz, 1H), 1.69−1.54 (m, 8H), 1.44 (s, 9H), 1.44−1.32 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.9, 155.1, 111.0, 80.1, 79.5, 78.7, 75.7, 63.3, 49.3, 36.6, 36.0, 28.3, 25.9, 24.9, 23.9, 23.7, 18.3, −5.4, −5.5. FT-IR (film): 3360, 2934, 2857, 1792, 1716, 1519, 1366, 1252, 1166, 837 cm^{-1}. HRMS (FAB^+, *m*/*z*): calcd for $C_{24}H_{44}NO_7Si$ ($M + H^+$), 486.2887; found, 486.2876. Anal. Calcd for $C_{24}H_{43}NO_7Si$: C, 59.38; H, 8.87; N, 2.89. Found: C, 59.46; H, 8.68; N, 2.87.

Desilylation of 9 To Produce the Primary Alcohol 10. To a solution of the silyl ether **9** (1.30 g, 2.68 mmol) in MeCN (80 mL) was added HF·Py (1.3 mL) dropwise at room temper-

ature. The resulting mixture was stirred at room temperature until TLC showed only a minor spot corresponding to the starting material [hexanes/EtOAc (6:4); silyl ether **9**, R_f 0.6; alcohol **10**, R_f 0.2]. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with saturated aq $NaHCO_3$ (100 mL), followed by brine. The aqueous layer was extracted with CH_2Cl_2 (100 mL). Organic layers were combined, dried over anhyd $MgSO_4$, and concentrated under reduced pressure. Most of the pyridine was removed under high vacuum at room temperature. Flash chromatography [70 g of silica, eluted with hexanes/EtOAc (65:35 → 1:1)] afforded pure **10** as a colorless foam (916 mg). Yield: 99% (on the basis of the recovered starting material). $[\alpha]^{22}_D$: −13.1 (*c* 3.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.49 (bs, 1H), 4.66−4.56 (m, 1H), 4.48 (t, J = 6.8 Hz, 1H), 4.15−4.09 (m, 2H), 3.94−3.88 (m, 1H), 3.74−3.67 (m, 1H), 2.92 (dd, J_1 = 8.0 Hz, J_2 = 18.0 Hz, 1H), 2.58 (dd, J_1 = 6.0 Hz, J_2 = 18.0 Hz, 1H), 1.90 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 1.69−1.54 (m, 8H), 1.45 (s, 9H), 1.44−1.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.0, 155.0, 110.8, 81.0, 79.8, 73.2, 61.8, 49.1, 36.4, 36.3, 35.5, 28.3, 24.9, 23.8. FT-IR (film): 3376, 2936, 2864, 1787, 1699, 1525, 1367, 1166, 1116, 1027 cm^{-1}. HRMS (FAB$^+$, *m*/*z*): calcd for $C_{18}H_{30}NO_7$ (M + H$^+$), 372.2022; found, 372.2030. Anal. Calcd for $C_{18}H_{29}NO_7$: C, 58.22; H, 7.82; N, 3.77. Found: C, 58.32; H, 7.58; N, 3.66.

Mitsunobu Cyclization of the *N*-Boc-Protected Amino Alcohol 10 To Produce the Piperidine 11a. A stirred solution of triphenylphosphine (98 mg, 0.37 mmol) in dry THF (1.5 mL) was treated with neat DEAD (46 μL, 0.29 mmol) at −20 °C under argon, and the resulting solution was kept at −15 °C for 20 min. The resulting pale yellow zwitterion solution was transferred using an additional portion of the dry THF (0.5 mL) into a solution of the amino alcohol **10** (73 mg, 0.195 mmol) in dry THF (6.0 mL) at −20 °C. The reaction mixture was allowed to reach room temperature, and its progress was monitored by TLC [hexanes/Et_2O (2:8); amino alcohol **10**, R_f 0.2; piperidine **11a**, R_f 0.6]. Once no further progress could be observed (3−5 h), a drop of water was added, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in a minimal amount of CH_2Cl_2 followed by a dilution with hexanes to effect the precipitation of a 1,2-dicarbethoxyhydrazine, which was subsequently removed by filtration. The crude mixture was loaded onto silica by concentrating it together with a dichloromethane/silica slurry under reduced pressure. Flash chromatography [5 g of silica, eluted with hexanes/EtOAc (7:3)] afforded pure **11a** as a colorless crystalline solid (57 mg). Yield: 82%. Mp: 173−174 °C (Et_2O/hexanes). $[\alpha]^{22}_D$: +42 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.08 (dd, J_1 = 3.2 Hz, J_2 = 7.6 Hz, 1H), 4.83−4.78 (m, 6 lines, 1H), 4.83−4.77 (m, 6 lines, 2H), 3.69 (dd, J_1 = 3.6 Hz, J_2 = 10.0 Hz, 1H), 3.38−3.31 (m, 7 lines, 1H), 3.01 (dd, J_1 = 8.8 Hz, J_2 = 19.2 Hz, 1H), 2.67 (dd, J_1 = 2.8 Hz, J_2 = 19.2 Hz, 1H), 1.77−1.56 (m, 8H), 1.46 (s, 9H), 1.44−1.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.8, 155.3, 113.8, 94.4, 81.5, 74.5, 67.5, 51.8, 47.7, 36.8, 36.4, 35.9, 28.2, 24.8, 23.7, 23.6. FT-IR (film): 2974, 2936, 2864, 1788, 1695, 1365, 1160, 1122 cm^{-1}. HRMS (FAB$^+$, *m*/*z*): calcd for $C_{18}H_{28}NO_6$ (M + H$^+$), 354.1917; found, 354.1939. Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.19; H, 7.65; N, 3.97. Found: C, 61.32; H, 7.50; N, 3.84.

Reductive Opening of the Lactone Ring in 11a To Produce the Piperidinediol 12. To a solution of the lactone **11a** (500 mg, 1.42 mmol) in dry THF (20 mL) cooled to −20 °C was added portionwise (0.50 mL each) ca. 1 M $LiAlH_4$ in THF (2.5 mL, 2.5 mmol). Once no further reaction progress could be observed [TLC; hexanes/EtOAc (1:1)] and most of the starting material (R_f 0.7) converted into the lactone **12** (R_f 0.2), leaving just a small amount of the intermediate lactol (R_f 0.4), the reaction mixture was quenched with EtOAc (0.3 mL) followed by a careful addition of $Na_2SO_4 \cdot 10H_2O$ at −20 °C. When the vigorous bubbling ceased, the reaction mixture was allowed to reach room temperature. The resulting slurry was passed through a Celite pad followed by thorough rinsing with THF. The filtrates were concentrated under reduced pressure and chromatographed [30 g of silica, eluted with CH_2Cl_2/EtOAc (7:3 → 4:6)] to afford pure **12** as a colorless crystalline solid (414 mg) along with the intermediate lactol (47 mg). The recovered lactol was reduced under the same conditions providing an additional amount of **12** (34 mg). Yield: 89%. Mp: 168−169 °C (CH_2Cl_2/hexanes). $[\alpha]^{22}_D$: +41 (*c* 0.85, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.53−4.44 (m, 2H), 4.14−4.05 (m, 9 lines, 1H), 3.78 (dd, J_1 = 6.4 Hz, J_2 = 12.0 Hz, 1H), 3.74−3.66 (m, 1H), 3.60 (dd, J_1 = 3.6 Hz, J_2 = 9.6 Hz, 1H), 3.53−3.44 (m, 2H), 2.97 (bs, 1H), 2.50 (bs, 1H), 2.19−2.09 (m, 8 lines, 1H), 1.85−1.77 (m, 10 lines, 1H), 1.74−1.58 (m, 8H), 1.46 (s, 9H), 1.46−1.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.7, 113.3, 81.0, 78.7, 68.3, 64.6, 59.1, 53.0, 47.4, 36.8, 36.2, 32.3, 28.3, 24.9, 23.8, 23.7. FT-IR (film): 3446, 2935, 2865, 1683, 1669, 1418, 1366, 1163, 1144, 1117 cm^{-1}. HRMS (FAB$^+$, *m*/*z*): calcd for $C_{18}H_{32}NO_6$ (M + H$^+$), 358.2230; found, 358.2221. Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.50; H, 8.68; N, 3.92. Found: C, 60.70; H, 8.53; N, 4.16.

Removal of the *N*-Boc/*O*,*O*-Dicyclohexylketal Protecting Groups in 12 To Produce 1-Deoxy-5-homogalactonojirimycin Hydrochloride (3). A solution of the *N*-Boc ketal **12** (114 mg, 0.319 mmol) in MeOH (15 mL) was treated with 1.4 M HCl in MeOH (6.5 mL, 9.0 mmol) and allowed to stand at room temperature overnight. Volatiles were removed under reduced pressure, and the oily residue recrystallized from MeOH/Et_2O to afford pure **3** as thin plates (64 mg). Yield: 94%. Mp: 167.5−168.5 °C (MeOH/Et_2O). $[\alpha]^{22}_D$: +24.8 (*c* 1.00, MeOH). ^{1}H NMR (D_2O, 400 MHz) δ: 4.15 (d, J = 2.0 Hz, 1H), 4.12−4.04 (m, 1H), 3.84−3.72 (m, 1H), 3.67 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 3.50 (AB, J_{AB} = 5.6 Hz, $\Delta\delta_{AB}$ = 9.0 Hz, 2H), 3.37 (s, 1H), 2.91 (t, J = 12 Hz, 1H), 2.04−1.92 (m, 2H). ^{13}C NMR (D_2O, 100 MHz) δ: 73.2, 68.4, 64.5, 57.8, 57.3, 46.5, 30.7. FT-IR (film): 3357, 2958, 2825, 2525, 1077, 1024 cm^{-1}. Anal. Calcd for $C_7H_{16}NO_4Cl$: C, 39.34; H, 7.49; N, 6.56; Cl, 16.63. Found: C, 39.70; H, 7.09; N, 6.25; Cl, 16.98.

***N*-Boc Lactone Diol 11b. 11b** was recrystallized from EtOAc/hexanes. The molecular structure was confirmed by X-ray analysis. Mp: 175 °C (dec). ^{1}H NMR (CD_3CN, 400 MHz) δ: 4.98 (q, J = 9.2 Hz, 1H), 4.65 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H), 3.98 (q, J = 4.4 Hz, 1H), 3.86−3.78 (m, 5 lines, 2H), 3.65 (d, J = 5.2 Hz, 1H), 2.63 (d, J = 13.6 Hz, 1H), 3.20 (d, J = 4.4 Hz, 1H), 2.64−2.41 (ABX, 8 lines, 2H), 1.44 (s, 9H). FT-IR (film): 3420, 2977, 2931, 1772, 1670, 1418, 1367, 1161 cm^{-1}. LRMS (FAB$^+$, *m*/*z*): 274 (M + H$^+$).

Lewis Acid Catalyzed Condensation To Produce the Homopropagylic Alcohol 13. To a solution of freshly prepared aldehyde (2.96 g, 7.15 mmol) in dry CH_2Cl_2 (7 mL) was added a solution of the allenylstannane **4** (3.42 g, 5.36 mmol) in dry CH_2Cl_2 (20 mL) at −70 °C under argon. To the resulting orange solution was added dropwise $BF_3 \cdot Et_2O$ (3.6 mL, 28 mmol) with good stirring over a period of 20 min. The stirring was continued at −70 °C for 25 h, and then the reaction mixture was quenched by a quick addition of saturated aq $NaHCO_3$ (25 mL), followed by an addition of CH_2Cl_2 (150 mL). The resulting slurry was stirred vigorously while it was allowed to warm slowly. The organic layer changed color from orange to light yellow upon reaching room temperature. The layers were separated, and the aqueous layer was extracted once with CH_2Cl_2 (100 mL). Combined organic solutions were washed with brine and dried over anhyd $MgSO_4$, and the solvent was removed under reduced pressure to afford 6.8 g of a yellowish semisolid. The crude material was loaded onto silica by concentrating a CH_2Cl_2 soln/silica slurry and chromatographed [100 g of silica, eluted with hexanes/Et_2O (8:2 → 1:1)] to afford pure **13** as a colorless oil (3.58 g). Yield: 90%. ^{1}H NMR ($CDCl_3$) δ: 7.42−7.24 (m, 10H), 7.10−7.00 (m, 6H), 6.94−6.86 (m, 4H), 5.77 (d, J = 7.5 Hz, 1H), 5.26 (d, J = 7.5 Hz, 1H), 5.10 (d, J = 6 Hz, 1H), 4.80−4.64 (m, 3H), 4.53 (d, J = 11.4 Hz, 1H), 4.2−4.1 (m, 2H), 3.98−3.86 (m, 2H), 3.86−3.76 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H), −0.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 158.3, 137.7, 137.5, 135.4, 134.1, 128.4, 128.3, 128.1,

127.9, 127.8, 127.6, 127.5, 126.1, 99.6, 92.1, 80.1, 79.8, 76.1, 73.7, 73.3, 72.5, 63.6, 62.1, 48.5, 26.0, −0.5, −5.3.

Lactonization of the Homopropargylic Alcohol 13 To Produce the Hydroxy Lactone 14. A solution of the alcohol **13** (38 mg, 50 μmol), $CuCl_2 \cdot 2H_2O$ (2.1 mg, 25 mol %), and $Pd(OAc)_2$ (1.2 mg, 10 mol %) in wet DMF (1% water, 0.50 mL) was stirred at room temperature under air atmosphere for 2 days. The solvent was removed under reduced pressure with gentle warming. The orange residue was taken-up in CH_2Cl_2/Et_2O (10:1) and washed with water. The organic layer was dried over anhyd $MgSO_4$ and concentrated in vacuo. Flash chromatography [hexanes/EtOAc (1:1)] afforded **14** as an off-white solid (14 mg). Yield: 47%. ^{1}H NMR ($CDCl_3$) Complex: see the Supporting Information. ^{13}C NMR ($CDCl_3$) δ: 173.4, 158.5, 137.7, 136.7, 133.1, 129.4, 128.8, 128.6, 128.4, 128.4, 128.2, 128.1, 127.5, 127.4, 125.6, 82.5, 81.4, 80.7, 79.7, 76.5, 72.6, 63.6, 60.1, 51.6, 32.8, 29.5.

Dess−Martin Oxidation of the Alcohol 14 To Produce the Aldehyde 15. To a stirred solution of the alcohol **14** (24 mg, 40 μmol) in dry CH_2Cl_2 (0.5 mL) was added Dess−Martin periodanane (25 mg, 59 μmol) in one portion at room temperature. The reagent went quickly into the solution. The resulting mixture turned milky-white within 40 min. The reaction progress was monitored by TLC [hexanes/EtOAc (1:1); alcohol, R_f 0.2; aldehyde **3**, R_f 0.4]. After 1.5 h, the reaction mixture was diluted with Et_2O and vigorously stirred with a mixture of saturated aq $NaHCO_3$ (1.25 mL) and saturated aq $Na_2S_2O_3$ (1.25 mL) until both layers became clear (ca. 10 min). The organic layer was separated, washed with brine, dried over anhyd $MgSO_4$, and concentrated under reduced pressure. Flash chromatography [hexanes/EtOAc (7:3 → 1:1)] afforded pure **15** as a cloudy oil (19 mg). Yield: 80%. ^{1}H NMR ($CDCl_3$) Complex: see the Supporting Information. ^{13}C NMR ($CDCl_3$) δ: 201.6, 172.7, 158.2, 136.8, 136.5, 135.2, 133.1, 128.9, 128.7, 128.6, 128.5, 128.4, 127.6, 127.5, 125.7, 99.8, 83.0, 81.4, 80.5, 78.3, 76.1, 74.5, 64.0, 60.4, 51.7, 32.9, 29.5, 21.1, 14.3.

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Note Added after ASAP Posting. The aldehyde structure in the TOC graphic contained an error in the version posted ASAP December 12, 2003; the corrected version was posted February 11, 2004.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5** and **13**−**15**; X-ray structural data for **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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