Stereocontrolled Lincomycin Synthesis

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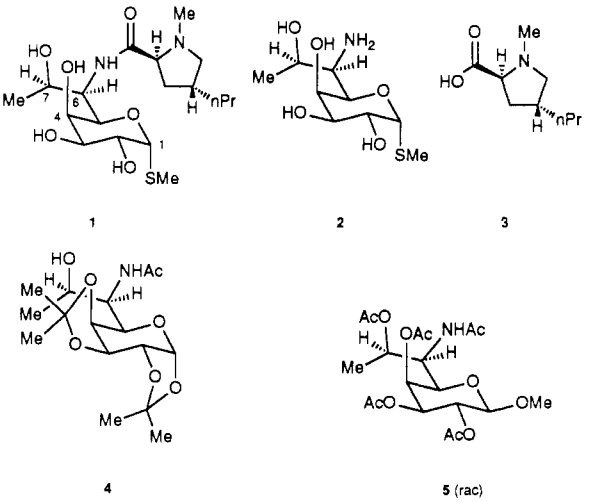
The synthesis from methyl α-D-galactopyranoside (**6**) of methyl thiolincosaminide (**2**), the direct synthetic precursor to lincomycin (**1**), is presented. The key step for controlling the off-pyranose stereocenters C-6 and C-7 is a novel intramolecular nitrogen delivery reaction using epoxy alcohol **10**. Reaction of **10** with dimethylcyanamide in the presence of sodium hydride and imidazole leads to the oxazoline **14**, a protected vicinal amino alcohol. The synthesis is completed by efficient exchange of acetal for thioacetal, followed by hydrolysis of the oxazoline and removal of the benzyl groups. The target **2** is obtained in 22 steps and 28% overall yield from **6**.

Lincomycin, **1**, is a commercial antibiotic used against bacterial infections in humans and animals.[1] It was first isolated at Upjohn in 1964 from cultures of *Streptomyces lincolnensis* var. *lincolnensis*.[2] Structural studies[3] showed that **1** is an N-acylated amino sugar consisting of two components: the amino octose thioglycoside **2**, termed methyl thiolincosaminide, and L-*trans*-*n*-propylhygric acid, **3**. Hydrazinolysis of **1** gave **2** and the hydrazide of **3**, and **2** and **3** could be joined to regenerate **1**.[4]

The first synthesis of **1** by Magerlein[5] began with the preparation of methyl 1-thio-α-D-galactopyranoside from galactose, and then chain extension by a Henry reaction, separation of isomers, and eventual coupling of **2** with **3** (which was also independently synthesized[6]). Szarek and co-workers[7] developed two routes to **2** from galactose derivatives which involved the late introduction of the thiomethyl group. Other groups[8] similarly have chain-extended galactose, functionalized C-6 and C-7, and ultimately intersected with the Szarek intermediate **4**. In spite of the considerable attention that has been given to the problem, none of these approaches provides even a modest amount of stereocontrol in the introduction of the functional groups at C-1, C-6, and C-7. Additionally, all the routes to **2** feature overall yields well below 1%.

A conceptually unique route to the *racemic* lincosamine derivative **5** was reported more recently by Danishefsky.[9] The synthesis of **5** from 1-methoxy-1-buten-3-one featured a Lewis acid promoted hetero-Diels–Alder reaction, and proceeded in about 22 steps and 2% overall yield. Significantly, the Danishefsky route provided the first instance of stereocontrolled introduction of the vicinal amino alcohol unit at C-6 and C-7, although multiple inversions of configuration at these positions were required. This



1 **2** **3**

4 **5 (rac)**

work also reveals the facility with which groups on C-4 participate in reactions at C-6.

The synthetic work on lincosamine derivatives, taken together, illustrates the very hindered nature of C-6 and the difficulty of introducing the amino group at this position. Our investigations of methods for intramolecular nitrogen delivery[10] led us to consider whether a nitrogen nucleophile tethered to the C-4 hydroxyl might be used to control both the site of introduction and the stereochemistry of the C-6 amino group. The epoxy alcohol **10** (Scheme I) provides the functionality required to test this hypothesis.

Epoxy alcohol **10** was synthesized from commerically available methyl α-D-galactopyranoside (**6**) by the route shown in Scheme I. Selective protection of the primary hydroxyl was best achieved using *tert*-butyldiphenylsilyl chloride.[11] Acetonide formation, followed by benzylation at the C-2 hydroxyl and desilylation,[11] gave the protected galactose **7**. Swern oxidation and triethylphosphonoacetate chain extension[12] gave an unsaturated ester, which was reduced to the alcohol using DIBAL, and then to the *trans*-alkene **8** by in situ reduction of the derived mesylate. Removal of the acetonide, selective benzylation at C-3,[13] and then benzoylation of the C-4 hydroxyl gave **9**. Finally, epoxidation of **9** using Danishefsky's protocol[14] (wherein the benzoyl carbonyl oxygen participates in bromohydrin formation, migrates to C-6, returns to C-4 during epoxide

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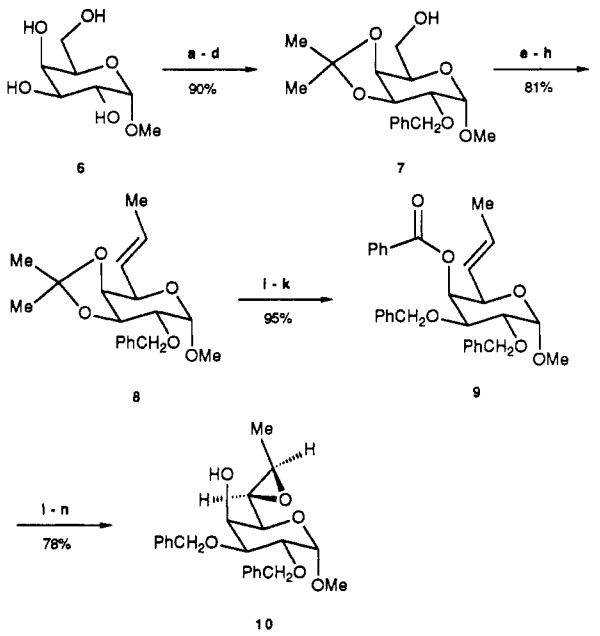
Scheme I. Synthesis of Epoxy Alcohol Substrate 10[a]

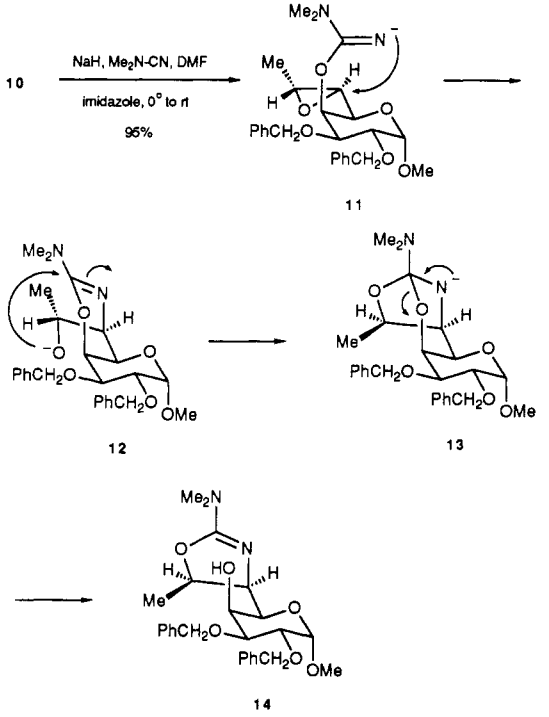


[a] Reagents: (a) *tert*-butyldiphenylsilyl chloride, py, room temperature; (b) dimethoxypropane, PPTS, acetone, reflux; (c) NaH, $PhCH_2Br$, THF, HMPA; (d) *n*-Bu_4NF, THF, room temperature; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (f) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, room temperature; (g) DIBAL, THF, (h) LDA, MsCl, $LiEt_3BH$, THF, −78 to 0 °C; (i) aqueous TFA, THF, room temperature; (j) *n*-Bu_2SnO, $PhCH_2Br$, *n*-Bu_4NI, PhH, reflux; (k) PhCOCl, py, room temperature; (l) NBS, H_2O, acetonitrile, room temperature; (m) DBU, PhH, room temperature; (n) aqueous NaOH, EtOH, room temperature.

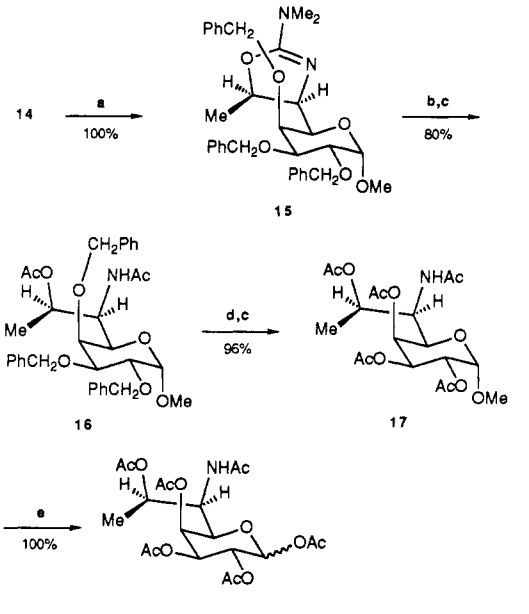
formation, and is finally removed by basic hydrolysis) led to the desired epoxide **10** as a single isomer with excellent overall efficiency. The experimental procedures for the reactions shown in Scheme I may be found in the supplementary material.

Two literature methods for intramolecular delivery of nitrogen from an epoxy alcohol precursor employ the alcohol-derived *N*-benzoylcarbamate[10,15] or the *N*-benzylcarbamate[16] anion, although neither has been reported to work for six-membered ring closure or in very hindered situations. In the case of **10**, attempted *N*-benzylcarbamate formation at the C-4 hydroxyl was unsuccessful, and the *N*-benzoylcarbamate was formed but upon base treatment merely gave back **10**. Similarly, treatment of the anion of **10** with substituted benzonitriles did not result in any epoxide opening. Giuliano's work on mercuricyclization of isoureas derived from an alcohol and *N,N*-dimethylcyanamide[17] suggested that the latter reagent might react in the desired fashion, and after considerable experimentation, we developed reaction conditions which gave the interesting condensation product **14** in high yield (Scheme II). Treatment of **10** as shown (the imidazole acts as a proton transfer catalyst[15]) leads, we infer, to an isourea anion **11**, which cyclizes with ring opening of the epoxide to give dihydrooxazine **12**. Spontaneous rearrangement of **12** through the diazaorthocarbonate intermediate **13** affords the more stable oxazoline **14**, as indicated by the C=N stretch[17] at 1657 cm^{-1} and the downfield shift of H-7 to δ 4.78. This novel cyclization/rearrangement sequence represents at present the best solution to the vexing problem of setting the off-pyranose stereochemistry in the lincosamine series.

Scheme II. Intramolecular Nitrogen Delivery



Scheme III. Synthesis of Lincosamine Hexaacetate[a]



[a] Reagents: (a) NaH, $PhCH_2Br$, DMF, room temperature; (b) KOH, ethylene glycol, reflux, 3 h; (c) Ac_2O, Et_3N, DMAP, py, room temperature; (d) H_2, $Pd(OH)_2$, MeOH, EtOAc, room temperature; (e) Ac_2O, H_2SO_4, 0 °C.

Conversion of oxazoline **14** to lincosamine hexaacetate **18**, a compound previously obtained by degradation of lincomycin,[4] is shown in Scheme III. Direct basic hydrolysis[17] of **14** could not be achieved, since the C-4 hydroxyl closed at C-7 to form a tetrahydrofuran under these

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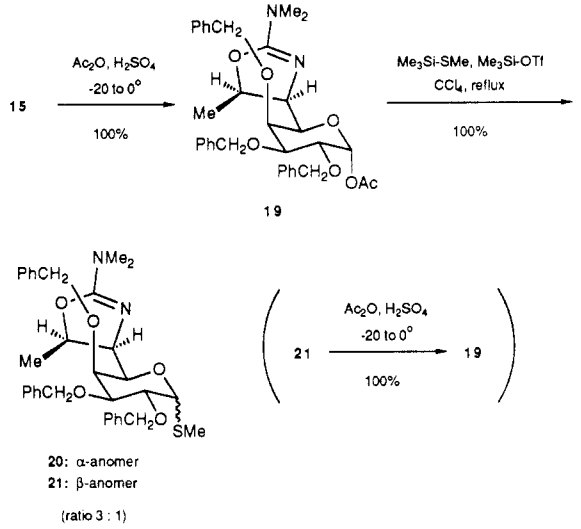
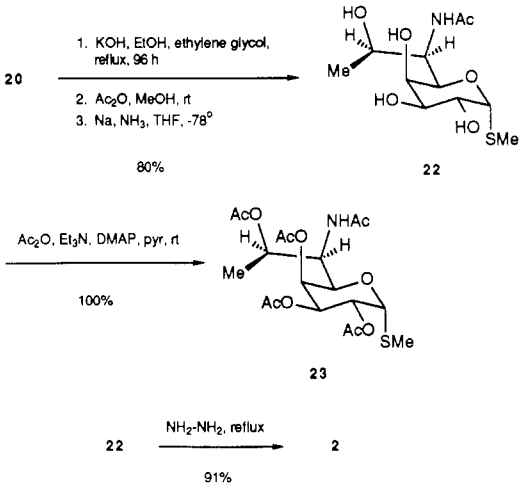
Scheme IV. Introduction of the Thiomethyl Group



Scheme V. Completion of the Synthesis



conditions. However, prior protection of the C-4 hydroxyl as its benzyl ether gave **15**, which underwent hydrolysis to the C-6, C-7 amino alcohol, conveniently isolated as its *N,O*-diacetate **16**. Hydrogenolysis of the benzyl groups and acetylation gave the pentaacetate **17**, a new lincosamine derivative (20 steps and 32% overall yield from **6**). Quantitative conversion of **17** to the hexaacetate **18** (1:1 mixture of anomers) occurred upon treatment of an acetic anhydride solution of **17** with a catalytic amount of sulfuric acid. Synthetic **18** was identical (TLC, 400-MHz ^{1}H NMR, and FT-IR) with authentic lincosamine hexaacetate[3] prepared by acetylation and acetic anhydride/sulfuric acid treatment of **2**.

There is no established means for introducing the methylthio group as the α-anomer at C-1 of **17** or **18**, since a participating acetyl group on the C-2 hydroxyl directs formation of the β-anomer. In addition, we found that the *N,O*-diacetate functionality at C-6/C-7 does not survive the Lewis acid conditions normally required for acetal exchange.[18,19] The solution to both of these problems lies in the availability of the oxazoline **15**, since a C-2 *O*-benzyl group would not be expected to participate in reactions at C-1, and the amino alcohol at C-6/C-7 is protected as a durable heterocycle. Scheme IV shows the conversion of **15** to the acetoxy glycoside **19** (α-anomer only), followed by replacement of the acetoxy group with methylthio using reaction conditions related to those suggested by Nicolaou,[19] giving a separable 3:1 mixture of the desired thioglycoside **20** and its β-anomer **21**. The efficiency of this acetal-to-monothioacetal exchange is noteworthy, and may represent the method of choice for the synthesis of other thioglycosides. The ratio of anomers **20:21** depends upon the reaction medium, with solvents more polar than carbon tetrachloride (dichloroethylene, methylene chloride, acetonitrile) giving more of the undesired β-anomer. In less polar solvent mixtures, such as carbon tetrachloride/pentane, the reaction did not proceed at a useful rate. The β-anomer **21** was also isolated and quantitatively reconverted to **19**, one cycle of which raised the effective level of stereocontrol at C-1 to 15:1 and the yield of **20** to 94% from **15**.

The synthesis of methyl *N*-acetylthiolincosaminide (**22**, Scheme V) was completed by hydrolysis of the oxazoline ring of **20**, N-acetylation, and removal of the benzyl groups. Further acetylation of **22** gave methyl thiolincosaminide pentaacetate, **23**. Comparison (TLC, 400-MHz ^{1}H NMR, FT-IR, mixed melting point, $[\alpha]_D$), of synthetic **23** with an authentic sample[4] prepared from lincomycin showed them to be identical. Finally, hydrazinolysis[7] of **22** gave in 91% yield methyl thiolincosaminide (**2**), matching the natural material. A measure of the efficiency of the synthetic route is that **2**, the direct precursor to **1**, is prepared in 22 steps and 28% overall yield (not counting the recycling of **21**) from commercially available methyl α-D-galactopyranoside (**6**). In addition, the functional groups at C-1, C-6, and C-7 are introduced with excellent stereocontrol using methodology which should find further application.

Experimental Section[20]

Methyl 2,3-Bis-*O*-(phenylmethyl)-6,8-dideoxy-7,6-(2-(*N*,*N*-dimethylamino)-1-oxa-3-azaprop-2-eno)-D-*erythro*-α-D-*galacto*-octopyranoside (14). A mixture of 400 mg (1.0 mmol) of **10** and 85 mg (1.25 mmol) of imidazole in 8 mL of dimethylcyanamide and 2 mL of DMF was added to a suspension of pentane washed sodium hydride (1.25 mmol) in 2 mL of DMF at 0 °C. The reaction mixture was stirred for 12 h at 0 °C and then for 48 h at room temperature. The reaction was quenched with 90 mg (1.25 mmol) of anhydrous sodium bicarbonate and concentrated. The residue was chromatographed on neutral alumina (Aldrich, activated, Brockmann I, 50 mesh) using ether as eluant to afford 470 mg of crude **14** which crystallized from methanol–water, and was recrystallized from ether. The product was obtained as white crystalline solid in 95% yield (447 mg), mp 88–91 °C: $[\alpha]$ +6.9°C (c = 0.510); NMR δ 1.34 (d, 3 H, J = 6), 2.88 (s, 6 H), 3.42 (s, 3 H), 3.73 (d, 1 H, J = 9), 3.84 (dd, 1 H, J = 10,3), 3.90 (dd, 1 H, J = 10,4), 4.19 (app t, 1 H, J = 9), 4.34 (d, 1 H, J = 3), 4.57 (d, 1 H, J = 4), 4.63 (d, 1 H, J = 12), 4.74 (app d, 2 H, J = 2), 4.77-4.79 (partially obscured m, 1 H), 4.84 (d, 1 H, J = 12), 7.25-7.39 (m, 10 H); IR 3439, 1657; CI-MS 471 (M^+ + 1). Anal. Calcd for $C_{26}H_{34}N_2O_6 \cdot 1/2H_2O$: C, 65.14; H, 7.31; N, 5.85. Found: C, 65.11; H, 7.18; N, 5.51.

Methyl 2,3,4-Tris-*O*-(phenylmethyl)-6,8-dideoxy-7,6-(2-(*N*,*N*-dimethylamino)-1-oxa-3-azaprop-2-eno)-D-*erythro*-α-D-*galacto*-octopyranoside (15). A solution of 235 mg (0.5 mmol) of **14** in 8 mL of DMF was added to a suspension of pentane-washed sodium hydride (1.0 mmol) in 2 mL of DMF containing 119 μL (1.0 mmol) of benzyl bromide. The reaction was stirred

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(19) (a) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430. (b) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189.

(20) A description of reagents and instrumentation used appears in the supplementary material and in Knapp, S.; Levorse, A. T.; Potenza, J. A. *J. Org. Chem.* **1988**, *53*, 4773. For several of the synthetic intermediates, we were unable to remove residual water by drying in vacuo at room temperature, and heating them caused partial decomposition. The elemental analyses are therefore reported with the fractional water component.

at room temperature for 12 h and then quenched with saturated aqueous sodium bicarbonate. The mixture was concentrated and partitioned between ethyl acetate and brine, dried, evaporated, and chromatographed using 1:12 acetone–petroleum ether as eluant to afford 280 mg (100%) of **15**. A sample crystallized from ether–petroleum ether as white needles, mp 85–86 °C: [α] +10.4° (c = 0.500); NMR δ 1.29 (d, 3 H, J = 7), 2.88 (s, 6 H), 3.42 (s, 3 H), 3.78 (d, 1 H, J = 11), 3.91 (dd, 1 H, J = 10, 2), 4.03 (dd, 1 H, J = 10,4), 4.22 (app t, 1 H, J = 11), 4.34 (br s, 1 H), 4.56 (d, 1 H, J = 4), 4.64 (d, 1 H, J = 12), 4.68 (d, 1 H, J = 12), 4.72–4.76 (m, 1 H), 4.76 (d, 1 H, J = 12), 4.82 (app d, 2 H, J = 12), 4.96 (d, 1 H, J = 12), 7.20–7.43 (m, 15 H); IR 1658; CI-MS 561 (M^+ + 1). Anal. Calcd for $C_{33}H_{40}N_2O_6$: C, 70.71; H, 7.14; N, 5.00. Found: C, 70.81; H, 7.25; N, 5.15.

Methyl 6-Acetamido-7-*O*-acetyl-2,3,4-tris-*O*-(phenylmethyl)-6,8-dideoxy-D-*erythro*-α-D-*galacto*-octopyranoside (16). A solution of 50 mg (0.089 mmol) of **15** and 2.67 mL of 1.0 M aqueous potassium hydroxide in 5 mL of ethylene glycol was heated at reflux for 3 h. The reaction was cooled and quenched with anhydrous sodium bicarbonate. The solvents were evaporated, and the residue was passed through silica (10 g) using THF as eluant to give the crude amino alcohol.

A mixture of this compound, 5.4 mg (0.045 mmol) of 4-(*N*,*N*-dimethylamino)pyridine, 2 mL of pyridine, 6 μL (0.045 mmol) of triethylamine, and 42 μL (0.445 mmol) of acetic anhydride was stirred at room temperature for 12 h, the solvent was evaporated, and the residue was chromatographed using 3:1 ether–petroleum ether as eluant to give 34 mg (65% overall from **15**) of **16**, mp 54–56 °C: [α] +63.8° (c = 0.980); NMR δ 1.18 (d, 3 H, J = 7), 1.62 (s, 3 H), 1.99 (s, 3 H), 3.35 (s, 3 H), 3.77–3.81 (m, 1 H), 3.86 (d, 1 H, J = 2), 3.98–4.05 (m, 2 H), 4.32 (ddd, 1 H, J = 9, 7, 7), 4.49 (d, 1 H, J = 10), 4.68 (d, 1 H, J = 12), 4.69 (d, 1 H, J = 4), 4.77 (q, 2 H, J = 9), 4.85–4.90 (m, 1 H), 4.88 (d, 1 H, J = 12), 5.18 (d, 1 H, J = 10), 6.59 (d, 1 H, J = 9), 7.22–7.34 (m, 15 H); IR 3293, 1735, 1654; CI-MS 592 (M^+ + 1). Anal. Calcd for $C_{34}H_{41}NO_8 \cdot {}^2/_9H_2O$: C, 68.57; H, 6.97; N, 2.35. Found: C, 68.55; H, 6.94; N, 2.63.

Methyl 6-Acetamido-2,3,4,7-tetra-*O*-acetyl-6,8-dideoxy-D-*erythro*-α-D-*galacto*-octopyranoside (17). A mixture of 5 mg of 20% palladium hydroxide on carbon, 20 mg (0.034 mmol) of **16**, 1 mL of ethyl acetate, and 2 mL of methanol was stirred vigorously under hydrogen (1 atm) for 12 h at room temperature. The catalyst was removed by filtration through Celite, and the solvents were evaporated to afford 11 mg of the debenzylated product.

A solution of this compound, 2 mg (0.017 mmol) of 4-(*N*,*N*-dimethylamino)pyridine, 2.4 μL (0.017 mmol) of triethylamine, and 32 μL (0.34 mmol) of acetic anhydride in 2 mL of pyridine was stirred at room temperature for 12 h and concentrated, and the residue was chromatographed using 5:1 ether–petroleum ether as eluant to give 14.6 mg (96%, overall from **16**) of **17**, mp 194–196 °C: [α] +148.2° (c = 0.515); NMR δ 1.28 (d, 3 H, J = 7), 1.89 (s, 3 H), 1.95 (s, 3 H), 2.03 (s, 3 H), 2.07 (s, 3 H), 2.11 (s, 3 H), 3.43 (s, 3 H), 3.93 (d, 1 H, J = 10), 4.53 (td, 1 H, J = 10, 2), 5.00 (d, 1 H, J = 4), 5.09–5.11 (m, 1 H), 5.12 (dd, 1 H, J = 11, 4), 5.26 (dd, 1 H, J = 11, 3), 5.38 (d, 1 H, J = 3), 5.47 (d, 1 H, J = 10); IR 3270, 1746, 1659; CI-MS 448 (M^+ + 1). Anal. Calcd for $C_{19}H_{29}NO_{11}$: C, 51.01; H, 6.49; N, 3.13. Found: C, 51.55; H, 6.59; N, 3.18.

6-Acetamido-1,2,3,4,7-penta-*O*-acetyl-6,8-dideoxy-D-*erythro*-α-D-*galacto*-octopyranose (18). A solution of 5 mg (0.011 mmol) of **17** in 1 mL of acetic anhydride was treated with sulfuric acid (5 μL) at 0 °C. The reaction was stirred for 30 min and then quenched by successive addition of anhydrous sodium carbonate and saturated aqueous sodium carbonate until gas evolution ceased. The product was taken up in ethyl acetate, washed twice with brine, dried, and concentrated to give a 1:1 mixture of α- and β-anomers quantitatively (5.3 mg). The α-anomer crystallized from ethyl ether (mp 194–197 °C) and was found identical (by TLC and 400-MHz ^1H NMR) to the hexaacetate α-anomer prepared from natural lincomycin (**1**): NMR of α-anomer δ 1.19 (d, 3 H, J = 6), 1.89 (s, 3 H), 1.97 (s, 3 H), 2.00 (s, 6 H), 2.12 (s, 6 H), 4.04 (d, 1 H, J = 10), 4.50 (td, 1 H, J = 10, 3), 5.00–5.04 (m, 1 H), 5.24–5.29 (m, 2 H), 5.37 (d, 1 H, J = 10), 5.43 (d, 1 H, J = 2), 6.36 (d, 1 H, J = 3); NMR of β-anomer (in mix with α) 1.22 (d, 3 H), 1.89 (s, 3 H), 1.97 (s, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.11 (s, 3 H), 2.13 (s, 3 H), 3.74 (d, 1 H, J = 10), 4.53 (td, 1 H, J = 10, 3), 4.97–5.02 (m, 1 H), 5.28–5.43 (m, 4 H), 5.57 (d, 1 H, J = 8).

1-*O*-Acetyl-2,3,4-tris-*O*-(phenylmethyl)-6,8-dideoxy-7,6-(2-(*N*,*N*-dimethylamino)-1-oxa-3-azaprop-2-eno)-D-*erythro*-α-D-*galacto*-octopyranose (19). A solution of 140 mg (0.25 mmol) of **15** in 5 mL of acetic anhydride was treated with 2.5 μL of sulfuric acid at −20 °C. The reaction was allowed to warm to 0 °C and quenced successively with anhydrous sodium carbonate and saturated aqueous sodium carbonate. The product was taken up in ethyl acetate, washed with brine, dried, and concentrated to afford pure **19** quantitatively (147 mg): [α] +33.9° (c = 0.685); NMR δ 1.17 (d, 3 H, J = 7), 2.07 (s, 3 H), 2.88 (s, 6 H), 3.80 (d, 1 H, J = 10), 3.89 (dd, 1 H, J = 10, 3), 4.15 (dd, 1 H, J = 10, 4), 4.21 (dd, 1 H, J = 10, 8), 4.39 (d, 1 H, J = 3), 4.68–4.75 (m, 5 H), 4.83 (d, 1 H, J = 11), 4.96 (d, 1 H, J = 11), 6.28 (d, 1 H, J = 4), 7.20–7.41 (m, 15 H); IR 1750, 1656; CI-MS 589 (M^+ + 1). Anal. Calcd for $C_{34}H_{40}N_2O_7 \cdot {}^2/_5H_2O$: C, 68.55; H, 6.85; N, 4.70. Found: C, 68.55; H, 6.81; N, 4.85.

Methyl 2,3,4-Tris-*O*-(phenylmethyl)-6,8-dideoxy-7,6-(2-(*N*,*N*-dimethylamino)-1-oxa-3-azaprop-2-eno)-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (20). A solution of 25 mg (0.0425 mmol) of **19**, 60 μL (0.425 mmol) of (methylthio)trimethylsilane, and 21 μL (0.106 mmol) of trimethylsilyl trifluoromethanesulfonate in 4 mL of carbon tetrachloride was heated at reflux for 3 h, cooled, and quenched with saturated aqueous sodium carbonate. The mixture was diluted with ethyl acetate, the layers were separated, and the organic layer was washed with saturated aqueous sodium carbonate and brine, dried, and concentrated. Chromatography using 1:12 acetone–petroleum ether as eluant afforded 18.4 mg (75%) of the α-anomer **20** and 6.1 mg (25%) of the β-anomer **21**. A sample of **20** crystallized from ether–hexane had mp 84–85 °C: [α] +61.9° (c = 0.425); NMR δ 1.28 (d, 3 H, J = 6), 2.13 (s, 3 H), 2.89 (s, 6 H), 3.65 (dd, 1 H, J = 10, 2), 4.03 (d, 1 H, J = 10), 4.23 (app t, 1 H, J = 10), 4.27 (dd, 1 H, J = 10, 6), 4.34 (br s, 1 H), 4.66–4.77 (m, 5 H), 4.83 (d, 1 H, J = 11), 4.96 (d, 1 H, J = 11), 5.11 (d, 1 H, J = 6), 7.19–7.40 (m, 15 H); IR 1657; CI-MS 577 (M^+ + 1). Anal. Calcd for $C_{33}H_{40}N_2SO_5 \cdot {}^3/_{10}H_2O$: C, 68.11; H, 6.98; N, 4.82; S, 5.51. Found: C, 68.12; H, 7.10; N, 4.78; S, 5.41. β-anomer **21**: NMR δ 1.26 (d, 3 H, J = 6), 2.19 (s, 3 H), 2.89 (s, 6 H), 3.29 (d, 1 H, J = 10), 3.55 (dd, 1 H, J = 9, 3), 3.80 (app t, 1 H, J = 9) 4.25–4.38 (m, 2 H), 4.28 (d, 1 H, J = 9), 4.61 (app d, 2 H, J = 3), 4.80–4.85 (m, 1 H), 4.81 (s, 2 H), 4.93 (q, 2 H, J = 11), 7.24–7.46 (m, 15 H); CI-MS 577 (M^+ + 1).

Methyl 6-Acetamido-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (22). A mixture of 50 mg (0.087 mmol) of **20**, 5.2 mL of absolute ethanol, 2.6 mL of ethylene glycol, and 2.6 mL of 1.0 M aqueous potassium hydroxide was heated at reflux for 96 h. The reaction was cooled and quenched with anhydrous sodium bicarbonate. The solvents were evaporated, and the residue was partitioned between ether and water. The organic layer was dried and concentrated to afford the crude amino alcohol.

A solution of this compound and 12.3 μL (0.130 mmol) of acetic anhydride in 5 mL of absolute methanol was stirred at room temperature for 3 h and then quenched with 21 μL (0.260 mmol) of pyridine. The mixture was concentrated and chromatographed using 4:1 ether–petroleum ether as eluant to give 39.5 mg (80%, overall from **20**) of the *N*-acetate, mp 72–75 °C: [α] +60.2° (c = 0.718); NMR δ 1.20 (d, 3 H, J = 6), 1.63 (s, 3 H), 2.06 (s, 3 H), 2.67 (d, 1 H, J = 5), 3.81 (dd, 1 H, J = 10, 2), 3.90–3.93 (m, 1 H), 3.96–3.99 (m, 1 H), 4.13 (d, 1 H, J = 2), 4.28–4.35 (m, 2 H), 4.55 (d, 1 H, J = 11), 4.69 (d, 1 H, J = 12), 4.75 (d, 1 H, J = 11), 4.78 (d, 1 H, J = 12), 4.91 (d, 1 H, J = 11), 5.15 (d, 1 H, J = 11), 5.38 (d, 1 H, J = 6), 6.43 (d, 1 H, J = 7), 7.26–7.42 (m, 15 H); IR 3391, 3290, 1656; CI-MS 566 (M^+ + 1).

A solution of 14 mg (0.025 mmol) of the *N*-acetyl amino alcohol in 1.5 mL of THF and 5 mL of distilled ammonia was treated with 9 mg (0.375 mmol) of freshly cut sodium metal at −78 °C. After 15 min the reaction was quenched with anhydrous ammonium chloride, and the solvents were evaporated. The product was taken up in methanolic (5%) THF, filtered, and concentrated to afford the debenzylated thioglycoside **22** (contaminated with some residual salts) which was identical by TLC and ^1H NMR with the natural material derived from **1**.

Methyl 6-Acetamido-2,3,4,7-tetra-*O*-acetyl-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (23). Peracetylation of **22** as for preparation of **17**, and chromatography using 4:1 ether–petroleum ether as eluant afforded 11.5 mg of **23** (quantitative yield for two steps), mp 213–214 °C; mixed melting point (with natural **23**, mp 215–216 °C) 213–214 °C; [α] +224° (*c* = 0.364, $CHCl_3$), lit.[4] +223° (*c* = 0.906, $CHCl_3$); NMR 1.26 (d, 3 H, *J* = 7), 1.90 (s, 3 H), 1.96 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 2.12 (s, 3 H), 4.24 (d, 1 H, *J* = 10), 4.57 (td, 1 H, *J* = 11, 2), 5.03 (qd, 1 H, *J* = 7, 2), 5.08 (dd, 1 H, *J* = 11, 3), 5.24 (dd, 1 H, *J* = 11, 6), 5.37 (d, 1 H, *J* = 3), 5.55 (d, 1 H, *J* = 11), 5.61 (d, 1 H, *J* = 6); IR 1750, 1649; CI-MS 464 (M^+ + 1).

Methyl 6-Amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (2). A solution of 50 mg (0.179 mmol) of **22** in 1.5 mL of hydrazine hydrate was heated at reflux for 3 h. The reaction mixture was cooled and concentrated, and the resulting white solid was recrystallized from 70% aqueous methanol–ether to afford 39 mg (91%) of **2**, mp 216–217 °C (with decomposition), mixed mp 216–217 °C (with **2** obtained from **1** by degradation, mp 216–217 °C, lit.[4] mp 225–228 °C): NMR (D_2O, 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt as internal reference) δ 1.15 (d, 3 H, *J* = 7), 2.13 (s, 3 H), 3.19 (dd, 1 H, *J* = 10, 4), 3.66 (dd, 1 H, *J* = 10, 3), 4.00 (d, 1 H, *J* = 9), 4.09–4.13 (m, 3 H), 5.33 (d, 1 H, *J* = 6).

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Registry No. **1**·HCl, 859-18-7; **2**, 14810-93-6; **3** hydrazide, 13380-37-5; **6**, 3396-99-4; **6** (1-*o*-silyl deriv), 114217-35-5; **6** (3,4-*o*-isopropylidene-6-*o*-silyl deriv), 114217-36-6; **7**, 27851-16-7; **7** (6-*o*-silyl deriv), 124780-61-6; **7** (6-aldehyde), 124780-62-7; **8**, 124780-53-6; **8** (8-uronic acid ethyl ester), 124780-63-8; **8** (8-alcohol), 124780-64-9; **8** (desisopropylidene deriv), 124780-65-0; **9**, 124780-54-7; **9** (4-*o*-debenzoyl deriv), 124780-66-1; **10**, 124780-55-8; **10** (4-*o*-benzoyl deriv), 124820-53-7; **14**, 124780-56-9; **15**, 124780-57-0; **16**, 124780-58-1; **17**, 124915-82-8; **17** (2,3,4-de-*o*-acetyl deriv), 124780-67-2; α-**18**, 6991-35-1; β-**18**, 6982-19-0; **19**, 124780-59-2; **20**, 124780-60-5; **21**, 124915-83-9; **22**, 6982-20-3; **22** (2,3,4,-tri-*o*-benzyl deriv), 124820-33-3; **23**, 13038-00-1.

Supplementary Material Available: Full experimental details for the preparation of epoxy alcohol **10** (Scheme I) and for the degradation of **1** leading to **2**, **18**, **22**, and **23** (5 pages). Ordering information is given on any current masthead page.

Development of a Fully Synthetic Stereoselective Route to 6-Deoxyerythronolide B by Reiterative Applications of the Lewis Acid Catalyzed Diene Aldehyde Cyclocondensation Reaction: A Remarkable Instance of Diastereofacial Selectivity†

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The synthesis of racemic **2**, which contains the relative stereochemistry appropriate to a synthesis of (9*S*)-dihydro-6-deoxyerythronolide B (see compound **38**), is described. The synthesis features three Lewis acid catalyzed diene aldehyde cyclocondensation reactions, using, in each instance, (*E*,*E*)-1-methoxy-2-methyl-3-(trimethylsilyloxy)penta-1,3-diene (**3**). In the first cycle, carried out with formaldehyde as the heterodienophile, a single stereogenic center is constructed (see compound **4**). By a series of steps featuring stereoselective reactions in pyranoid matrices, as well as two additional cyclocondensation reactions, the stereogenicity of C_2 (erythronolide numbering) is used to induce the required configurations at carbons 3, 4, 5, 6, 8, 9, 10, and 11 of the target system (see formation of glycal **20**). To achieve stereoselectivity from this point onward, it was necessary to open the pyranoid substructure with attendant loss of configuration at C_{11} (see *E* enal **31**). Subsequently, the configurations required at carbons 11, 12, and 13 to reach compound **2** were introduced in highly selective reactions, carried out on acyclic intermediates. The enantiomerically homogeneous (9*S*) version of compound **2** was obtained from 6-deoxyerythronolide (**1**) by way of tetraol **38**. Compound **2** (9*S*) was converted to **1**, again by way of **38**. Macrolactonization (17% yield) was carried at the stage of seco acid **44** to produce **45**, which was, in turn, converted to **1**. A totally synthetic route to **1** is thus accomplished in a formal sense.

Introduction

In 1981 we began to investigate the potentialities of the Lewis acid catalyzed diene aldehyde cyclocondensation (LACDAC) process as a device for the assembly of a variety of goal structures.[1,2] The new chemistry has been of value in addressing the total synthesis of targets bearing multiple stereogenic centers such as pyranoid antibiotics[3,4] and complex monosaccharides.[5,6] An important element in the applicability of the method has been the finding that the stereochemical outcome of the cyclocondensation is re-

† Dedicated to the contributions of Professor Satoru Masamune in the macrolide field.

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