Use of a Novel α-Hydroxyethylating Reagent in the Stereoselective Synthesis of Lincosamine

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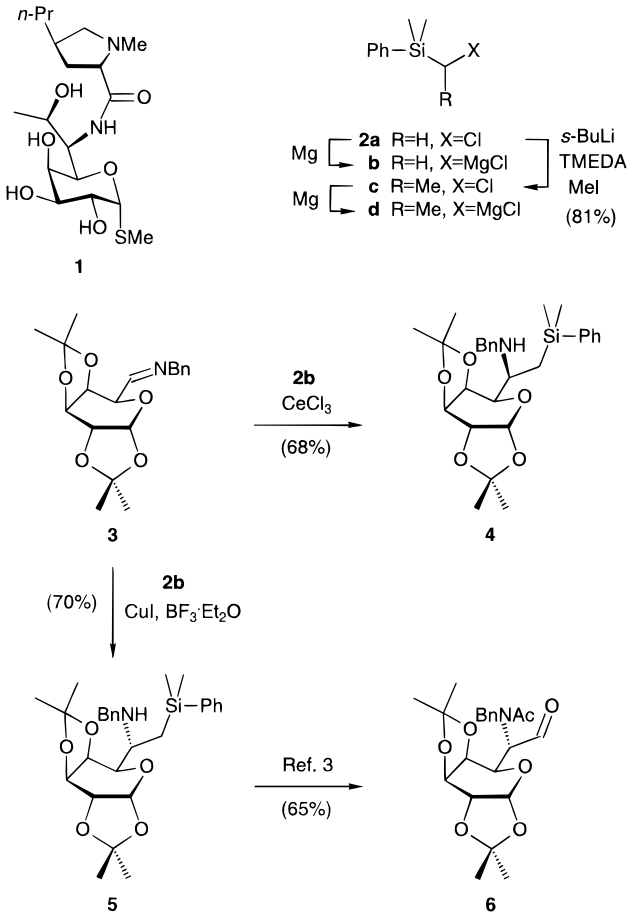
Received October 31, 1995

Earlier work from our[1] and other[2] laboratories amply demonstrated that [(dimethylphenylsilyl)methyl]magnesium chloride (**2b**) is an effective reagent for the stereoselective hydroxymethylation of aldehyde[1a−d] or hemiacetal[1e] functions in carbohydrates. Further studies revealed[3] (Scheme 1) that addition of **2b**, precomplexed with cerium(III) chloride, to 6-(benzylimino)-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**) led to the exclusive formation of the *syn*-adduct **4**. On the other hand, complete reversal of stereochemistry was attained by executing the same reaction with the corresponding organocopper reagent, prepared *in situ* by precomplexation of **2b** with CuI and $BF_3{\cdot}Et_2O$. The resulting *anti*-adduct **5** could then be transformed into α-amino aldehyde **6**, which is a known[4] precursor of lincosamine (*i.e.*, 6-amino-6,8-dideoxy-D-*erythro*-D-*galacto*-octose), the sugar component of the antibiotic lincomycin (**1**).[5,6] It is evident, however, that conversion of aldehyde **6** into lincosamine demands the creation of an additional chiral center at C_7 by stereoselective methylation. The stereochemical outcome of the copper(I)-mediated condensation of **2b** with **3** stimulated us to find out whether the required stereocenters could be introduced in one step by α-hydroxyethylation of **3** with the secondary Grignard reagent [1-(dimethylphenylsilyl)ethyl]magnesium chloride (**2d**).

The requisite Grignard reagent **2d** was readily accessible from commercially available (chloromethyl)dimethylphenylsilane (**2a**) by the procedure depicted in Scheme 1. Thus, consecutive α-deprotonation[7] and methylation of **2a** afforded crude (1-chloroethyl)dimethylphenylsilane

Scheme 1



(**2c**). Workup of the reaction mixture, followed by purification on silica gel and then distillation, gave racemic **2c** in more than 95% purity, as gauged by proton NMR spectroscopy. Metalation of **2c** with magnesium gave the requisite secondary Grignard reagent **2d**. At this stage, a solution of the benzylimine derivative **3** in THF was added dropwise to a cooled (−70 °C) suspension of the organocopper derivative of **2d** (2.5 equiv), prepared[8] by sequential complexation of **2d** with stoichiometric amounts of copper(I)iodide and $BF_3{\cdot}Et_2O$. The reaction mixture was kept at −70 °C for 1 h and slowly warmed to −20 °C, and the reaction was quenched with excess triethylamine. Extractive workup and purification by silica gel column chromatography gave, as evidenced by high-resolution NMR spectroscopy, a homogeneous and diastereomerically pure product in 84% yield. The newly introduced C_6 and C_7 stereocenters in the β-amino silane adduct were established to have the respective *S* and *R* configuration as in **7** (Scheme 2) by its transformation into the known[9] protected lincosamine derivative **11**. In order to avoid N-oxidation during unmasking of the silyl moiety in the next step, the amino group was further protected with a benzyloxycarbonyl group (**7** → **8**). Unmasking of fully protected **8** with KBr in peracetic acid[10] afforded amino alcohol **9** in 82% yield. Conversion of **9** into **11** was accomplished by the following two-step

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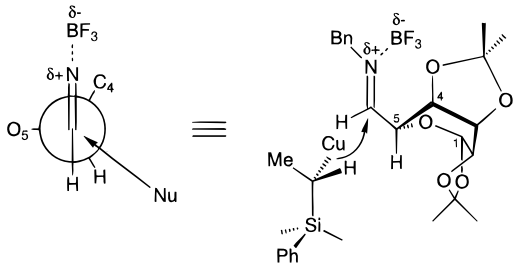
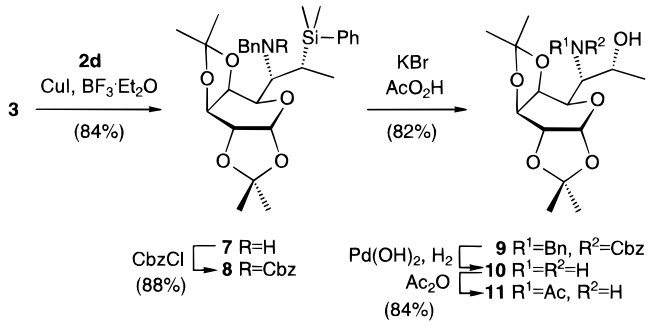


Figure 1. Schematic presentation of the Felkin−Anh model for nucleophilic addition of **2d** to imine **3** (left) and the presumed in space orientation of reactants (right).

Scheme 2



procedure. Hydrogenolysis of benzyl- and benzyloxycarbonyl protecting groups and subsequent selective N-acetylation of **10** under Schotten−Bauman conditions gave **11** in an overall yield of 84% after purification. The thus obtained product was in all aspects identical (melting point, optical rotation, NMR data) to the same compound prepared previously.[9]

The excellent stereoselectivity observed in the condensation of **2d** and **3** can be rationalized as follows. It may be assumed that the condensation of imine **3** with the organocopper reagent derived from **2d**, as in the copper(I)-mediated *anti*-addition of **2b** to **3**, proceeds according to the Felkin−Anh model[11] (Figure 1). In line with this model, aldimine **3** adopts a conformation[12] having a torsion angle of −90° between the C−N double bond and the ring oxygen (O_5). Attack of the nucleophile occurs from the sterically least hindered side, *i.e.*, the *re* face of the imine. However, the orientation of **2d** in the sterically most favorable transition state geometry is strongly influenced by the bulkiness of its substituents.[13,14] It is most likely that in a matched pair transition state the least hindered position will be occupied by the sterically most congested silyl moiety (Figure 1). In addition, an *exo*-like orientation of the methyl group in the nucleophile will minimize steric interactions with the sugar.

In conclusion, compound **10**, which is a valuable intermediate in the synthesis of lincomycin, has been prepared in a highly efficient and protracted route using the readily accessible α-hydroxyethylating reagent **2d**. The latter result presents, to the best of our knowledge, the first example of the successful application of a secondary organocopper reagent in the diastereoselective addition to a chiral imine.[13,14]

Experimental Section

Materials. (Chloromethyl)dimethylphenylsilane was obtained from Aldrich Chemical Co. and used as received. Benzylimine **3** was freshly prepared from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside[15] by Swern oxidation and treatment with benzylamine, followed by flash chromatography. Light petroleum ether had a boiling point fraction of 40−60 °C.

(1-Chloroethyl)dimethylphenylsilane (2c). (Chloromethyl)dimethylphenylsilane (9.02 mL, 50 mmol) in dry THF (80 mL) at −78 °C under nitrogen was treated with *s*-BuLi (42.3 mL, 1.3 M), followed by TMEDA (8.3 mL, 55 mmol). After the mixture was kept at this temperature for 40 min, the solution was warmed (−40 °C) and MeI (3.42 mL, 55 mmol) added. After 30 min, the reaction mixture was allowed to warm to rt, the reaction was quenched with a 15% NH_4Cl solution (50 mL), and the solution was extracted with light petroleum ether (200 mL). The organic layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (light petroleum ether) and vacuum distillation to afford **2c** as a colorless liquid: yield 8.05 g (81%), bp 52−54 °C (15 mmHg). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.58−7.33 (m, 5H), 3.53 (q, 1H, J = 7.5 Hz), 0.71 (d, 3H, J = 7.5 Hz), 0.27, 0.25 (2 × s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.0, 134.1, 129.6, 127.8, 44.9, 20.0, −5.0, −6.2. Anal. Calcd for $C_{10}H_{15}ClSi$ (M 198.77): C, 60.43; H, 7.61; Cl, 17.84; Si, 14.13. Found: C, 60.40; H, 7.74.

6-(Benzylamino)-6,7,8-trideoxy-7-(dimethylphenylsilyl)-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (7). Under an argon atmosphere, a suspension of magnesium powder (0.34 g, 13.8 mmol) in refluxing THF (2 mL) was activated by addition of a few drops of 1,2-dibromoethane. Next, a solution of (1-chloroethyl)dimethylphenylsilane (**2c**, 2.38 g, 12.5 mmol) in THF (10 mL) was added at such a rate as to maintain a gentle reflux. The thus obtained Grignard was kept at 40 °C for 1 h before addition of additional THF (10 mL) and cooling to −40 °C. Under a stream of argon, solid CuI (2.38 g, 12.5 mmol) was added with vigorous stirring, which was continued another 30 min. The heterogeneous mixture was cooled to −70 °C, and $BF_3{\cdot}Et_2O$ (1.53 mL, 12.5 mmol) was added. After 5 min, a solution of **3** (1.74 g, 5.0 mmol) in THF (5 mL) was added slowly to the mixture which was kept at −70 °C for 1 h before slow warming to −20 °C. The reaction was quenched with excess triethylamine, and the solution was poured into a vigorously stirred solution of 15% NH_4Cl (30 mL). Diethyl ether (100 mL) was added, and the organic layer was washed with water (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The oily product was applied onto a column of silica gel and eluted with light petroleum ether followed by ether/light petroleum ether/triethylamine (20/80/1 → 40/60/1 → 60/40/1, v/v/v). Concentration of the appropriate fractions afforded **7** as an oil: yield 2.15 g (84%); R_f 0.4 (ether/light petroleum ether/triethylamine, 70/30/1, v/v/v); $[\alpha]^{20}_D$ −38.8 (*c* 1, $CHCl_3$). MS (*m*/*z*): 512 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.56−7.12 (m, 10H, H-arom), 5.55 (d, 1H, H-1, $J_{1,2}$ = 5.2 Hz), 4.58 (d, 1H, H-3, $J_{3,4}$ = 8.1 Hz), 4.49 (d, 1H, H-4), 4.26 (dd, 1H, H-2, $J_{2,3}$ = 1.5 Hz), 3.89, 3.67 (AB, 2H, CH_2, Bn, J = 12.7 Hz), 3.61 (d, 1H, H-5, $J_{5,6}$ = 9.4 Hz), 3.13 (dd, 1H, H-6, $J_{6,7}$ = 2.1 Hz), 1.73 (dq, 1H, H-7, $J_{7,8}$ = 7.6 Hz), 1.50, 1.45, 1.33, 1.31 (4 × s, 12H, CH_3, isoprop), 1.00 (d, 3H, H-8), 0.37, 0.35 (2 × s, 6H, CH_3, Si). ^{13}C-{^{1}H} NMR ($CDCl_3$): δ 141.1, 138.7, 133.8, 128.7−126.6, 108.4, 107.8, 96.7, 71.2, 71.1, 70.7, 67.8, 53.3, 25.9, 25.8, 24.7, 24.2, 20.6, 7.4, −3.4, −3.9. Anal. Calcd for $C_{29}H_{41}NO_5Si$ (M 511.74): C, 68.07; H, 8.08; N, 2.74; Si, 5.49. Found: C, 67.31; H, 8.04; N, 2.68.

6-(*N*-(Benzyloxycarbonyl)benzylamino)-6,7,8-trideoxy-7-(dimethylphenylsilyl)-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (8). Compound **7** (2.0 g, 3.91 mmol) was dissolved in a mixture of dioxane (20 mL) and water (10 mL). The solution was cooled (0 °C) and treated with

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$NaHCO_3$ (0.71 g, 9.8 mmol) and benzyl chloroformate (0.73 mL, 4.3 mmol). After 5 min, the mixture was allowed to reach rt and stirred for 1 h. After this time, TLC analysis (toluene/ethyl acetate, 5/1, v/v) indicated the complete conversion of **7** into a more lipophilic product. The mixture was concentrated *in vacuo*, and the residue was redissolved in diethyl ether and extracted with water. The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (toluene/ethyl acetate, 10/1 → 5/1 → 3/1 → 1/1, v/v) to give **8** as a colorless oil: yield 2.22 g (88%); R_f 0.7 (toluene/ethyl acetate, 5/1, v/v); $[\alpha]^{20}_D$ −37.6 (*c* 2, $CHCl_3$). MS (*m*/*z*): 646 $[M + H]^+$, 668 $[M + Na]^+$. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 58 °C): δ 139.0, 136.3, 133.0−126.9, 108.4, 108.3, 96.4, 71.2, 70.4, 67.0, 64.8, 59.4, 25.8, 24.8, 23.9, 20.8, −2.4. Anal. Calcd for $C_{37}H_{47}NO_7Si$ (M 645.87): C, 68.81; H, 7.34; N, 2.17; Si, 4.35. Found: C, 68.51; H, 7.38; N, 2.10.

6-(*N*-(Benzyloxycarbonyl)benzylamino)-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (9). Acetic acid (30 mL), sodium acetate (3.2 g, 3.9 mmol), and potassium bromide (0.45 g, 3.8 mmol) were added to **8** (2.05 g, 3.17 mmol), and the mixture was stirred until the salts were dissolved. The solution was cooled (10 °C), and peracetic acid (15.9 mL, 30% in acetic acid) was added dropwise under exclusion of light. After the mixture was stirred for 3 h at 20 °C, TLC analysis (toluene/ethyl acetate, 5/1, v/v) indicated complete conversion of the starting material into a more hydrophilic product (R_f 0.3). The mixture was diluted with diethyl ether (100 mL) and poured into a cooled (0 °C) solution of sodium thiosulfate (30 mL, 10%). The organic layer was washed with aqueous $NaHCO_3$ and treated with solid $NaHCO_3$ until no more gas evolved. The layers were separated, and the organic layer was extracted with water (20 mL). The residue was dissolved in toluene (2 × 10 mL) and concentrated before it was applied onto a column of silica gel, which was eluted with toluene/ethyl acetate (95/5 → 85/15, v/v). Concentration of the appropriate fractions afforded **9** as an oil: yield 1.37 g (82%); R_f 0.3 (toluene/ethyl acetate, 5/1, v/v); $[\alpha]^{20}_D$ −63.4 (*c* 1, $CHCl_3$). MS (*m*/*z*): 528 $[M + H]^+$. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 58 °C): δ 156.1, 137.6, 136.2, 128.7−127.3, 108.8, 96.2, 70.7−69.9, 67.2, 54.1, 25.8, 25.7, 24.8, 24.1, 20.0. Anal. Calcd for $C_{29}H_{37}NO_8$ (M 527.62): C, 66.02; H, 7.07; N, 2.66. Found: C, 66.02; H, 7.11; N, 2.74.

6-Amino-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (10). Compound **9** (0.57 g, 1.08 mmol) was dissolved in methanol (6 mL), and after addition of anhydrous $Pd(OH)_2$ (0.1 g), the suspension was kept under an atmosphere of hydrogen (1 atm) for 1 h, after which time TLC analysis indicated the complete disappearance of **9** and the formation of a highly hydrophilic product. The catalyst was removed by filtration over Celite and washed with methanol. The combined filtrates were concentrated under reduced pressure, and traces of methanol were removed by coevaporation with CH_2Cl_2 to give **10** as a white solid: yield 0.33 g (100%); mp 74−76 °C; R_f 0.2 (ethyl acetate/methanol, 19/1, v/v); $[\alpha]^{20}_D$ −51.9 (*c* 2, $CHCl_3$). MS (*m*/*z*): 304 $[M + H]^+$, 326 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.51 (d, 1H, J = 5.1 Hz), 4.62 (dd, 1H, J = 8.0, 2.5 Hz), 4.44 (dd, 1H, J = 8.0, 1.8 Hz), 4.32 (dd, 1H, J = 5.1, 2.5 Hz), 4.03 (dq, 1H, J = 6.4, 4.8 Hz), 3.59 (dd, 1H, J = 9.1, 1.8 Hz), 3.13 (dd, 1H, J = 9.1, 4.8 Hz), 1.53, 1.46, 1.36, 1.33 (4 × s, 12H), 1.18 (d, 3H, J = 7.4 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 108.8, 108.2, 96.1, 70.8, 70.3, 70.0, 68.4, 66.8, 54.4, 25.6, 25.5, 24.5, 24.2, 16.2. Anal. Calcd for $C_{14}H_{25}NO_6$ (M 303.36): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.23; H, 8.39; N, 4.51.

6-Acetamido-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (11). To a stirred solution of **10** (102 mg, 0.34 mmol) in a mixture of dioxane (2 mL) and water (2.5 mL) were added consecutively $NaHCO_3$ (67 mg, 0.85 mmol) and acetic anhydride (0.032 mL, 0.68 mmol). The mixture was stirred for 1 h after which time all starting material had disappeared. The mixture was concentrated, acetic anhydride was coevaporated with toluene (3 × 2 mL), and the residue was applied onto a column of silica gel. Elution with ethyl acetate afforded a colorless oil, which was crystallized from diethyl ether to give **11** as white crystals: yield 98 mg (84%); mp 166−167 °C (lit.[9] mp 166−167 °C); R_f 0.4 (ethyl acetate/methanol, 19/1, v/v); $[\alpha]^{20}_D$ −51.4 (*c* 2, $CHCl_3$) (lit.[9] −53). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.53 (d, 1H, J = 5.0 Hz), 4.61 (dd, 1H, J = 8.0, 2.3 Hz), 4.45 (dd, 1H, J = 8.0, 1.1 Hz), 4.30 (dd, 1H, J = 5.0, 2.3 Hz), 4.17−4.10 (m, 1H), 4.03 (m, 1H), 2.91 (d, 1H, J = 4.5 Hz), 1.99 (s, 3H), 1.73 (br s, 1H), 1.52, 1.50, 1.35, 1.32 (4 × s, 12H), 1.24 (d, 3H, J = 6.4 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 170.6, 109.1, 108.7, 96.5, 71.8, 70.8, 70.4, 68.2, 65.2, 56.4, 25.8, 24.8, 24.1, 23.3, 19.8. Anal. Calcd for $C_{16}H_{27}NO_7$ (M 345.39): C, 55.64; H, 7.88; N, 4.06. Found: C, 55.60; H, 7.91; N, 4.01.

JO951931+