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Stereocontrolled Hydroxymethylation of Carbohydrate Imines: Formal Synthesis of Destomic Acid and Lincosamine

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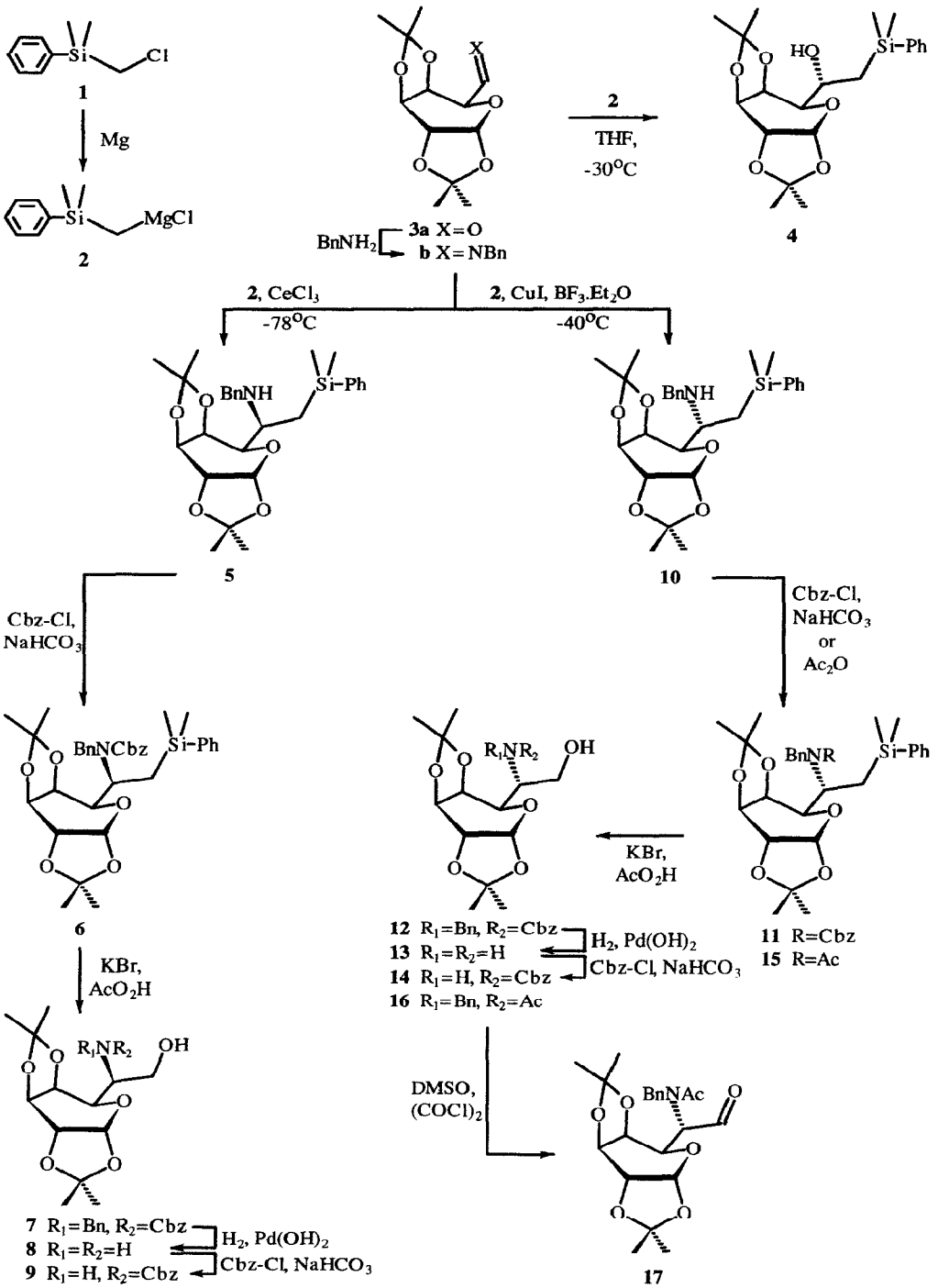
Abstract: Addition of [(dimethylphenylsilyl)methyl]magnesium chloride to 6-benzylimino-6-deoxy-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose mediated by $Ce(III)Cl_3$ or $CuI/BF_3{\cdot}Et_2O$ proceeds with complete *syn*- or *anti*-diastereoselectivity, respectively, to afford highly chiral precursors of destomic acid or lincosamine.

Earlier studies from our[1] and other[2] laboratories revealed that Grignard derivative **2**, derived from commercially available (chloromethyl)dimethylphenylsilane (**1**), is an effective reagent for the hydroxymethylation of aldehyde or hemiacetal functions in carbohydrates. In most cases, the nucleophilic addition of **2** proceeds[1a-d] with high diastereoselectivity resulting in the formation of the *syn*-hydroxysilane adduct. On the other hand, condensation of **2** with the α-D-galacto-hexodialdo-1,5-pyranoside derivative **3a** led predominantly[1c] to the *anti*-adduct **4**, further elaboration of which gave the earlier prepared[3b] 6,7-*epimino* precursor of destomic acid.

As part of an ongoing program to widen the scope of the hydroxymethylating reagent **2**, we here report that the addition of organocerium or copper reagents of **2** to the galactose imine derivative **3b** results in the exclusive formation of the respective *syn*- or *anti*-adducts **5** and **10**, which can be readily transformed into the known[3] precursors **9** and **14** of destomic acid and lincosamine.

Recent studies by Reetz[4a] and Terashima[4b] showed that the nucleophilic addition of organocerium reagents to imine functions is superior, in terms of both yield and stereoselectivity, over the traditional organolithium and magnesium reagents. The high promise of this methodology stimulated us to investigate the stereochemical outcome of the addition reaction of the hydroxymethylating reagent **2** to galactose imine **3b**. To this end isomerically pure[5] imine **3b**, readily accessible by the reaction of benzylamine with aldehyde **3a**, was treated with excess Grignard reagent **2**, precomplexed with cerium(III)chloride[6] (Et_2O/THF, -78°C → 0°C). Proton NMR analysis of the crude product revealed the presence of one diastereoisomer. Work-up and purification by silica gel column chromatography afforded the pure stereoisomer in 68% yield. The newly introduced C-6 stereocenter of the resulting product was unambiguously established to have the R-configuration, as in the *syn*-adduct **5**[7], by its conversion into the reported[3] precursor **9** of destomic acid. Thus, benzyloxycarbonylation of **5** was followed by smooth conversion of the resulting urethane **6** into alcohol **7** by oxidative unmasking of the silyl moiety[8,9] (KBr, CH_3CO_3H, 71% yield). Hydrogenolysis of both N-protecting groups using Pearlman's catalyst gave the

Scheme 1


1
Mg
2
3a X=O
b X=NBn
BnNH2
2
THF,
-30°C
4
2, CeCl3
-78°C
2, CuI, BF3.Et2O
-40°C
5
10
Cbz-Cl,
NaHCO3
Cbz-Cl,
NaHCO3
or
Ac2O
6
11 R=Cbz
15 R=Ac
KBr,
AcO2H
KBr,
AcO2H
12 R1=Bn, R2=Cbz
13 R1=R2=H
14 R1=H, R2=Cbz
16 R1=Bn, R2=Ac
H2, Pd(OH)2
Cbz-Cl, NaHCO3
7 R1=Bn, R2=Cbz
8 R1=R2=H
9 R1=H, R2=Cbz
H2, Pd(OH)2
Cbz-Cl, NaHCO3
DMSO,
(COCl)2
17

free amino derivative **8**, which was treated with benzyl chloroformate under Schotten-Bauman conditions to afford homogeneous **9** (64% yield based on **7**), which was in all aspects identical ($[\alpha]_D$, NMR) with an authentic sample[3]. The observed *syn*-stereoselectivity is probably due to complexation of the cerium(III) salts with the nitrogen and the α-oxygen atoms[10] in **3b**, thus directing the incoming nucleophile to the less sterically hindered *si* face of the imine.

In order to synthesize lincosamine, the sugar component of the antibiotic lincomycin[11], it was imperative that the nucleophilic addition of **2** to the imine derivative **3b** would follow the Felkin-Anh[12] model, leading to the *anti*-hydroxysilane adduct. Recently, it was shown[4b] that nucleophilic addition of organocopper(I) reagents in the presence of $BF_3{\cdot}Et_2O$[13] gives the *anti*-adduct in high diastereomeric excess. Hence, precomplexation of Grignard reagent **2** with CuI (ether, -40°C) and $BF_3{\cdot}Et_2O$ (-78°C) was followed by the addition of imine **3b** and slow warming to -40°C, to give a sole adduct, as revealed by proton NMR analysis. After work-up and purification, *anti*-adduct **10** was isolated in 70% yield. The *anti*-selectivity of the addition reaction was corroborated *via* transformation of **10** into compound **14**[3] (41% overall yield) following the same four step procedure (**10**→**14**) described earlier for the preparation of **9** from **5**. Moreover, **10** could be effectively converted into α-amino aldehyde **17**, a suitable precursor[14] of lincosamine, by the following three-step procedure. Thus, acetylation of **10** (→**15**) and oxidative unmasking of the silyl moiety in **15** (→**16**) gave, after Swern oxidation, aldehyde **17** (65% overall yield), the spectroscopic data of which were in full accord with those of the same compound prepared by Matsui[14a] as well as Dondoni[14b].

In conclusion, the results presented in this paper indicate that the cerium and copper derivatives of the Grignard reagent **2** show great promise[15] for the future asymmetric synthesis of β-amino alcohols, which are key structural elements of nitrogen containing natural products, such as amino sugars, sphingolipid bases, amino acids and β-lactams.

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7. New compounds were fully characterized by spectroscopic techniques (^{1}H and ^{13}C NMR) and their molecular formulas were established by high resolution mass spectrometry. Relevant ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (50.1 MHz, $CDCl_3$) data of the compounds **5** and **9** are as follows: **5**: ^{1}H NMR δ 5.55 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.56 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.30 (dd, 1H, H-2), 4.28 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 3.77 (dd, 1H, H-5, $J_{5,6}$ 9.0 Hz), 3.22 (ddd, 1H, H-6, $J_{6,7a}$ 9.8 Hz, $J_{6,7b}$ 4.2 Hz), 1.40 (m, 1H, H-7a), 1.06 (m, 1H, H-7b), 0.40, 0.37 (2x CH_3-Si). ^{13}C NMR δ 96.5 (C-1), 71.4, 71.1, 70.4, 69.6 (C-2, C-3, C-4, C-5), 53.4 (C-6), 15.9 (C-7), -1.6, -2.2 (2x CH_3-Si). MS (thermospray) m/z 376 $[M+H]^+$. **10**: ^{1}H NMR δ 5.56 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.55 (dd, 1H, H-3, $J_{2,3}$ 2.0 Hz, $J_{3,4}$ 8.0 Hz), 4.46 (dd, 1H, H-4, $J_{4,5}$ 1.4 Hz), 4.27 (dd, 1H, H-2), 3.56 (dd, 1H, H-5, $J_{5,6}$ 7.7 Hz), 3.04 (m, 1H, H-6), 1.42 (dd, 1H, H-7a, $J_{6,7a}$ 5.1 Hz, $J_{7a,7b}$ 3.8 Hz), 0.95 (m, 1H, H-7b), 0.35, 0.31 (2x CH_3-Si). ^{13}C NMR δ 96.4 (C-1), 71.6, 70.9, 70.6 (C-2, C-3, C-4, C-5), 54.0 (C-6), 19.2 (C-7), -1.8, -2.6 (2x CH_3-Si). MS (thermospray) m/z 376 $[M+H]^+$.
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15. Preliminary experiments indicated that the addition of organocerium or copper reagents derived from vinylmagnesium bromide to the imine **3b** proceeded with the same stereochemistry as observed for the corresponding organometallic derivatives of the Grignard reagent **2**.

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