Interception of an Iminium Ion Equivalent by Intramolecular Nucleophilic Attack by a Silyl Ether during Lithium Aluminium Hydride Reduction of a Tertiary Lactam

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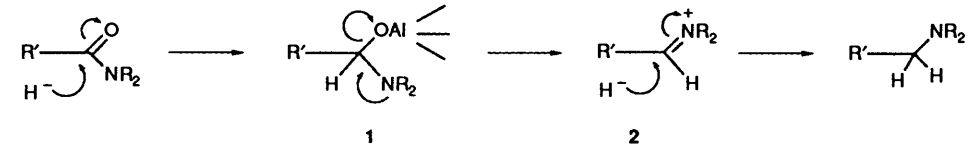
The efficient formation of a bicyclic oxazolidine by lithium aluminium hydride reduction of a tertiary amide provides an example of intramolecular nucleophilic capture of an iminium ion equivalent by the oxygen of a silyl ether.

Lithium aluminium hydride is the classic reagent for the reduction of tertiary amides to tertiary amines.[1,2] The commonly accepted mechanism[3] for the reduction involves initial attack by hydride at the carbonyl to give a tetrahedral *O*-aluminate complex (**1**) as an intermediate,[4] which subsequently fragments to produce an iminium ion (**2**) which is finally attacked by a further hydride equivalent (Scheme 1).[5] There is, however, little direct evidence for the intermediacy of an iminium ion, since any potential nucleophilic trap of such a species would have to compete with the tetrahydroaluminate ion or its equivalent. This paper provides an example of the interception of such an iminium cation or equivalent species by intramolecular nucleophilic attack by the oxygen of a silyl ether to give a bicyclic oxazolidine, successfully competing with further attack by hydride which would have resulted in the formation of the anticipated tertiary amine.

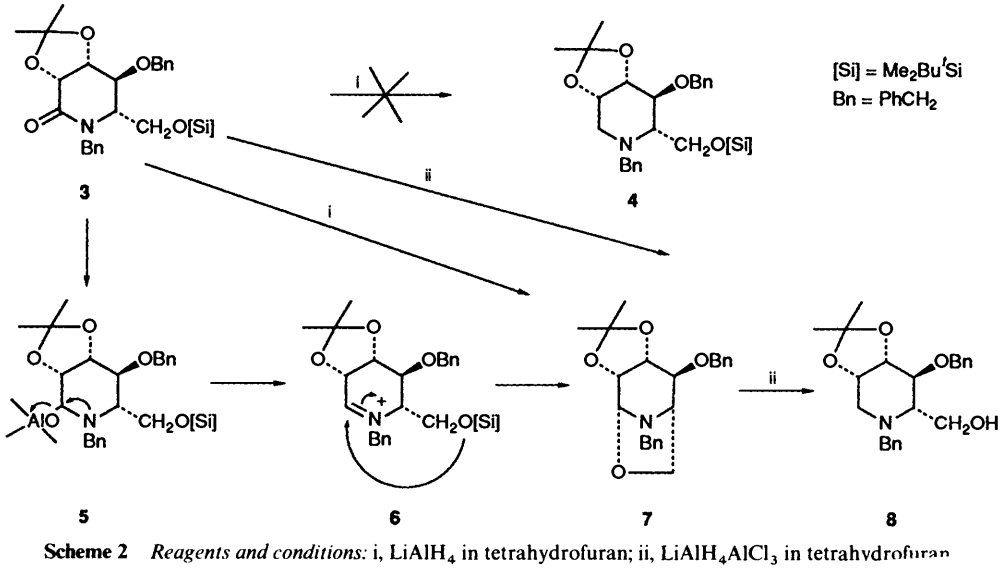
During the course of the synthesis of some stereoisomers of castanospermine,[6,7] it was necessary to reduce the fully protected mannonolactam **3** to the corresponding amine **4**. When the protected tertiary amide **3** was reacted with lithium aluminium hydride in tetrahydrofuran, only trace amounts of the expected piperidine **4** were formed; the major product, isolated in 72% yield, had lost the silyl ether protecting group and its mass spectrum showed a molecular weight consistent with the oxazolidine **7**. Thus, the reaction probably proceeds by addition of hydride to the carbonyl to give a tetrahedral adduct **5** which fragments to give the iminium ion **6** or its equivalent; the iminium ion **6** is then attacked intramolecularly by the oxygen of the C-6 *tert*-butyldimethylsilyl ether to afford the oxazolidine **7**, rather than by external hydride. The oxazolidine **7** is reduced in good yield by lithium aluminium hydride in tetrahydrofuran with addition of aluminium trichloride as a Lewis acid to give the piperidine **8**; treatment of the lactam **3** with lithium aluminium hydride in tetrahydrofuran in the presence of aluminium trichloride gives the desilylated tertiary amine **8** directly in 82% yield. The structure of the oxazolidine **7** has further been established by its elaboration into L-deoxymannojirimycin (**10**). Hydrogenolysis of the oxazolidine in methanol in the presence of palladium black followed by removal of the isopropylidene protecting group by hydrolysis in aqueous trifluoroacetic acid gave L-deoxymannojirimycin (**10**) identical with an authentic sample.[8]

In order to investigate the role of the 6-*O*-*tert*-butyldimethylsilyl protecting group in the reaction, a sample of the lactam **3**



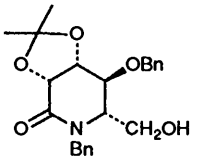
1 **2**

Scheme 1



3 **4** **5** **6** **7** **8**

Scheme 2 *Reagents and conditions:* i, $LiAlH_4$ in tetrahydrofuran; ii, $LiAlH_4AlCl_3$ in tetrahydrofuran



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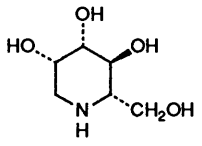

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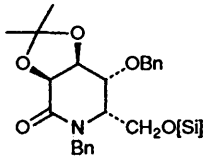

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was treated with tetrabutylammonium fluoride in tetrahydrofuran to give the desilylated lactam **9** in 80% yield. Reduction of **9** with lithium aluminium hydride in tetrahydrofuran gave the oxazolidine **7** in only moderate yield (40%), together with an approximately equal amount of the fully reduced amine **8** (44%). This implies that, in the corresponding iminium ion intermediate derived from **9**, the species derived from the unprotected C-6 hydroxy group is not as effective a nucleophile as is the silyl ether, this is reasonable since the free hydroxy group will have reacted with, and thus become highly complexed to, species derived from the tetrahydroaluminate ion. This complex is presumably an inferior source of intramolecular nucleophilic oxygen.

In summary, this paper reports the reduction of the lactam **3** by lithium aluminium hydride to the oxazolidine **7** in good yield, providing an example of the trapping of an intermediate iminium ion **6** or its equivalent by an intramolecular nucleophile which has successfully competed with external hydride. It does not appear that this interception of iminium ions is general; when the lactam **11** [9]—which is epimeric at C-5 with the enantiomer of **3**—was reduced with lithium aluminium hydride, the corresponding tertiary amine was formed in excellent yield; no oxazolidine could be isolated.

Experimental

Melting points were recorded on a Kofler hot block. ^{1}H NMR spectra were recorded on Varian Gemini 200 (at 200 MHz), Bruker WH 300 (300 MHz), or Bruker AM 500 (500 MHz) spectrometers and ^{13}C NMR spectra were recorded on Varian Gemini 200 (50 MHz) or Bruker 250 (62.9 MHz) spectrometers. Multiplicities were assigned using the DEPT sequence on the Gemini and by off-resonance decoupling on the Bruker. IR spectra were recorded on Perkin-Elmer 297 or 781 spectrophotometers. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250, or Trio-1 GCMS (DB-5 column) spectrometers using desorption CI (NH_3), EI and CI (NH_3) techniques, as stated. Optical rotations were measured with a Perkin-Elmer 241 polarimeter (1 dm path length) and are given in units of 10^{-1} cm^2 deg g^{-1}. Microanalyses were performed at the Dyson–Perrins Laboratory. TLC was performed with $60F_{254}$ silica with detection 5% conc. sulfuric acid in methanol, 0.2% cerium (IV) sulfate and 5% ammonium molybdate in 2 mol dm^{-3} sulfuric acid, and 0.5% ninhydrin in methanol. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Solvents were purified as described elsewhere.[7] *N*,4-*O*-dibenzyl-6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-L-mannono-δ-lactam (**3**), m.p. 72–73 °C, and an authentic sample of L-deoxymannojirimycin were prepared as previously described.[7]

N,4-O-*Dibenzyl*-2,3-O-*isopropylidene*-L-*mannono*-δ-*lactam* (**9**).—The fully protected δ-lactam **3** (42 mg, 0.08 mmol) was dissolved in tetrahydrofuran (5 cm^3) and 1 mol dm^{-3} tetrabutylammonium fluoride in tetrahydrofuran (160 mm^3, 0.16 mmol) was added. The reaction was left to stand for 2 h at room temperature. Solvents were removed under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate–hexane 3:2) to give *N*,4-*O*-dibenzyl-2,3-*O*-isopropylidene-L-mannono-δ-lactam (**9**) (26 mg, 80%), oil, $[\alpha]_D^{20}$ −55.1 (*c* 0.55 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3400br (OH) and 1640 (C=O); δ_C($CDCl_3$) 166.9 (s, Cl), 137.3, 136.6 (2 × s, Ar), 128.7, 128.5, 128.0, 127.9, 127.7 (5 × d, Ar), 110.2 [s, $C(CH_3)_2$], 75.2, 73.4, 72.2 (3 × d, C2, C3, C4), 71.3 (t), 62.1 (t), 59.0 (d, C5), 48.8 (t) and 25.7, 23.4 [2 × q, $C(CH_3)_2$]; δ_H($CDCl_3$) 7.40–7.00 (10 H, m, Ar), 5.41 (1 H, d), 4.69 (1 H, d), 4.51 (1 H, m), 4.20 (3 H, m), 3.70 (4 H, m) and 1.52, 1.34 [2 × s, $C(CH_3)_2$].

1,6-*Anhydro*-N,4-O-*dibenzyl*-1,5-*dideoxy*-1,5-*imino*-2,3-O-*isopropylidene*-L-*mannopyranose* (**7**).—(*a*) Via *reduction of the fully protected lactam* **3**. Lithium aluminium hydride (26 mg, 0.66 mmol) was added to a solution of the δ-lactam **3** (167 mg, 0.33 mmol) in dry tetrahydrofuran (10 cm^3) and the reaction mixture was stirred under dry nitrogen for 2 h. The reaction was quenched by addition of saturated aqueous sodium sulfate (5 cm^3) and the aqueous phase extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (magnesium sulfate) and the solvents removed under reduced pressure. Purification by flash column chromatography (ethyl acetate–hexane 1:5) gave the oxazolidine **7** (86 mg, 72%), oil, $[\alpha]_D^{20}$ −48.8 (*c* 1.0 in $CHCl_3$); *m*/*z* (ACE NH_3) 382 (M + H$^+$, 100%); δ_C($CDCl_3$) 139.2, 138.9 (2 × s, Ar), 128.9, 128.4, 128.0, 127.6, 127.3 (5 × d, Ar), 109.2 [s, $C(CH_3)_2$], 93.9 (s, Cl), 79.2, 75.9 (3 × d, C2, C3, C4), 71.0 (t, C6), 62.3 (t, ArCH_2O), 60.2 (d, C5), 57.1 (t, ArCH_2N) and 26.6, 26.1 [2 × q, $C(CH_3)_2$]; δ_H($CDCl_3$) 7.50–7.30 (10 H, m, Ar), 4.76 (1 H, d, H1, J = 3.1 Hz), 4.46 (2 H, dd, ArCH_2O), 4.28 (1 H, d, J = 6.6 Hz), 4.20 (1 H, dd, J = 3.2 Hz, 6.6 Hz), 3.90–3.50 (6 H. m) and 1.57, 1.34 [2 × s, $C(CH_3)_2$].

(*b*) Via *reduction of the desilylated lactam* **9**. The dibenzyl δ-lactam **9** (21 mg, 0.05 mmol) was dissolved in dry tetrahydrofuran (10 cm^3) and lithium aluminium hydride (4 mg, 0.1 mmol) was added. The reaction was then stirred under dry nitrogen for 2 h. The reaction was quenched by addition of saturated aqueous sodium sulfate (5 cm^3) and the aqueous phase extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (magnesium sulfate) and the solvents removed under reduced pressure. Purification by flash column chromatography (ethyl acetate–hexane 1:5) gave the oxazolidine **7** (8 mg, 40%), and the tertiary amine **8** (9 mg, 44%) (data for **8** is given below).

N,4-O-*Dibenzyl*-1,5-*dideoxy*-1,5-*imino*-2,3-O-*isopropylidene*-L-*mannitol* (**8**).—(*a*) *Directly from the silylated lactam* (**3**). The fully protected δ-lactam **3** (3.00 g, 5.4 mmol) was dissolved in dry tetrahydrofuran (50 cm^3) and lithium aluminium hydride (413 mg, 10.8 mmol) was added. The reaction was stirred under dry nitrogen for 15 min when TLC (ethyl acetate–hexane 1:5) showed no starting material (R_f = 0.2) and one major product (R_f = 0.3). Aluminium trichloride (720 mg, 5.4 mmol) was added and the reaction mixture was stirred for a further 15 min when TLC (ethyl acetate–hexane 1:5) showed one major product (R_f = 0.4). The reaction mixture was quenched with saturated sodium sulfate solution (25 cm^3). The two phases were separated and the aqueous phase was washed with dichloro-

methane (3 × 25 cm^3). The organic phases were combined and dried (magnesium sulfate) and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate–hexane 1:3) to yield *N*,4-*O*-dibenzyl-1,5-dideoxy-1,5-imino-2,3-isopropylidene-L-mannitol (**8**), a colourless oil (1.73 g, 82%), $[\alpha]_D^{20}$ −6.9 (*c* 1.56 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3300br (OH); *m*/*z* (DCI NH_3) 384 ($M + H^+$) and 352 ($M - MeOH + H^+$); $\delta_C(CDCl_3)$ 138.6, 138.5 (2 × s, Ar), 129.1, 128.6, 128.1, 128.0, 127.5 (5 × d, Ar), 109.3 [s, $C(CH_3)_2$], 78.0 (d), 76.7 (d), 72.8 (t), 72.3 (d), 62.8 (d), 60.5 (t), 57.2 (t), 49.2 (t) and 27.5, 25.4 [2 × q, $C(CH_3)_2$]; $\delta_H(CDCl_3)$ 7.32 (10 H, m, Ar), 4.85, 4.66 (2 H, AB system, $ArCH_2O$), 4.32 (2 H, m), 3.98, 3.60 (2 H, AB system, $ArCH_2N$), 3.80 (3 H, m), 2.93 (1 H, dd), 2.71 (3 H, m) and 1.55, 1.37 [2 × 3 H, 2 × s, $C(CH_3)_2$] (Found: C, 71.95; H, 7.45; N, 3.45. $C_{23}H_{29}NO_4$ requires C, 72.06; H, 7.57; N, 3.65%).

(*b*) *From the oxazolidine* **7**. Lithium aluminium hydride (9 mg, 0.23 mmol) and aluminium trichloride (30 mg, 0.23 mmol) were added to a solution of the oxazolidine **7** (85 mg, 0.22 mmol) in dry tetrahydrofuran (5 cm^3) and stirred under dry nitrogen. After 15 min, TLC (ethyl acetate–hexane 1:3) showed no starting material (R_f = 0.5) and one product (R_f = 0.4). The reaction was quenched by addition of saturated aqueous sodium sulfate (5 cm^3) and the aqueous phase extracted with ethyl acetate (3 × 5 cm^3). The combined organic extracts were dried (magnesium sulfate) and the solvents removed under reduced pressure. Purification by flash column chromatography (ethyl acetate–hexane 1:3) gave the amine **8** (57 mg, 67%), identical with that prepared by method (*a*).

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