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Selective reduction of *N*-protected-α-amino lactones to lactols with lithium tri-*tert*-butoxyaluminohydride

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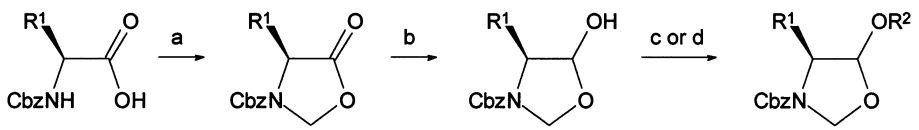
Abstract—α-Amino lactols **3** can be prepared in good yield and high optical purity by reduction of α-amino lactones **2** with lithium tri-*tert*-butoxyaluminohydride ($LiAlH(O\text{-}t\text{-}Bu)_3$).

Optically active *N*-protected α-amino aldehydes are important intermediates for the preparation of amino alcohols and peptide analogues of biological interest.[1] Moreover, recently published papers revealed that some of the peptide *C*-terminal aldehydes are crucial components of potent inhibitors of interleukin converting enzyme and calpain.[2] However, α-amino aldehydes cannot be purified by chromatography nor be stored at room temperature for some time because these compounds racemize easily on silica gel and at room temperature. In order to overcome these problems, *N*-carbobenzyloxy α-amino lactols (hemiacetals) **3** have been used as the precursor or equivalents of the corresponding α-amino aldehydes by some research groups. For example, Kim and Iyengar independently reported the reduction and alkylation of various lactols to the corresponding alcohols.[3] Although diisobutylaluminum hydride (DIBAL-H) and sodium borohydride have been used by these chemists to prepare lactols from the corresponding α-amino lactones, we found that these two reagents and the reaction conditions were not reproducible in our hands. Over-reduction and/or unidentified compounds instead of the desired lactols **3** were the major products. Herein, we report that lithium tri-*tert*-butoxyaluminohydride ($LiAlH(O\text{-}t\text{-}Bu)_3$) is a more efficient and selective reagent than DIBAL-H or sodium borohydride for the reduction of lactones **2** to lactols **3**.

Lactones **2** were prepared according to a procedure in the literature.[4] Reduction of lactones **2** with 1.2 equiv. of $LiAlH(O\text{-}t\text{-}Bu)_3$ at −78°C for 10 min followed by



	R¹	R²
1a	CH_3	
1b	$CH_2CH(CH_3)_2$	
1c	$CH(CH_3)_2$	
1d	$CH_2C_6H_5$	
1e	C_6H_5	
2a	CH_3	
2b	$CH_2CH(CH_3)_2$	
2c	$CH(CH_3)_2$	
2d	$CH_2C_6H_5$	
2e	C_6H_5	
3a	CH_3	
3b	$CH_2CH(CH_3)_2$	
3c	$CH(CH_3)_2$	
3d	$CH_2C_6H_5$	
3e	C_6H_5	
4a	CH_3	$C(O)CH_3$
4b	CH_3	CH_3

Scheme 1. *Reagents and conditions*: (a) see Ref. 4; (b) 1.0 M lithium tri-*tert*-butoxyaluminohydride in THF (1.2 equiv.), tetrahydrofuran, −78°C, 10 min, then 0–18°C, 6–24 h, 80–87%; (c) acetic anhydride, *N*-methylmorpholine, dichloromethane, 0–18°C, 2 h, 90%; (d) methyl iodide, silver(I) oxide, 0–18°C, 4 days, 80–90%.

Keywords: chiral α-amino lactol; lithium tri-*tert*-butoxyaluminohydride.

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stirring at 0–18°C for 6–24 h gave the desired lactols **3** (Scheme 1). The pure lactols **3** were obtained as a viscous liquid in 80–90% yield after chromatography over silica gel (Table 1).[5] We observed that LiAlH(O-*t*-Bu)$_3$ is very mild and gives reproducible yields. No lactone **2** was reduced if the reaction was performed at −78°C overnight. The reductions were completed within six hours at 0–18°C, but the yields were not influenced even if the solution was stirred at this temperature overnight. Only a trace amount of unreacted lactone **2** and/or overreduction product(s) were detected by TLC under these reaction conditions. However, the amount of the over-reduced compound(s) significantly increased if LiAlH(O-*t*-Bu)$_3$ was added to a lactone solution in an ice bath or even at room temperature. No racemization was observed during the chromatography process because the specific rotation value of the lactol **3a** purified by chromatography is higher than that of the crude compound. It is also noticeable that the lactols **3** obtained from the LiAlH(O-*t*-Bu)$_3$ reduction in this study have higher specific rotation values than those obtained from the sodium borohydride reduction.[3c] Although the optical purity of these lactols **3** did not significantly change after storage at room temperature for several days, however, cold storage is strongly recommended to avoid any possible deterioration and/or oxidation. Of course, conversion of the hemiacetal (e.g. **3a**) to the corresponding acetal (e.g. **4a** or **4b**) should be more suitable for prolonged storage at room temperature. The specific rotation value of acetal **4b** showed that the optical purity was nearly unchanged after storage at room temperature for several months.

In summary, we have demonstrated that LiAlH(O-*t*-Bu)$_3$ reduction of α-amino lactones **2** provided the corresponding α-amino lactols **3** in good yield, selectivity, and optical purity. These lactols **3** were quite stable and can be stored at low temperature for some time without loss of optical purity.

General procedure

To a stirring tetrahydrofuran solution of 0.25 g (0.9 mmol) of lactone **2b** in an acetone dry ice bath was added dropwise a 1.0 M solution of LiAlH(O-*t*-Bu)$_3$ in THF (1.1 mL, 1 mmol). The solution was stirred at this temperature for 10 min, then moved to an ice bath and stirred at 0–18°C for 6–24 h. After the reduction was complete (monitored by TLC), the solution was quenched with a 20% citric acid solution (5 mL) in an ice bath. The suspension was concentrated to remove tetrahydrofuran. The residue was extracted with ethyl acetate several times. The organic layer was combined, washed with brine, dried over magnesium sulfate, filtered, and concentrated. Purification by chromatography over silica gel (hexane/ethyl acetate 4:1) provided 0.20 g (80%) of pure lactol **3b** as a pale yellow oil.[5]

Table 1.

Entry	Compound	Yield of **3** from **2** (%)	$[\alpha]_D^{22}$ (*c* g/100 mL, solvent)
1	**3a**	80	−19.4 (*c* 1, $CHCl_3$)
2	**3b**	80	−9.4 (*c* 1, $CHCl_3$)
3	**3c**	87	−23.8 (*c* 1, $CHCl_3$)
4	**3d**	80	−51.6 (*c* 1, $CHCl_3$)
5	**3e**	83	+9.4 (*c* 1, $CHCl_3$)
6	**4a**	90 (from **3a**)	−37.5 (*c* 2, $CHCl_3$)
7	**4b**	90 (from **3a**)	−35.4 (*c* 2, $CHCl_3$)

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5. Characterization data of lactols **3a**–**e**:
   3a: oil; $[\alpha]_D^{22}$ −19.4 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.30 (s, 1H), 5.22–5.10 (m, 3H), 5.06 (s) and 4.96 (d, *J*=4.3 Hz, total 1H), 4.01 (m, 1H), 3.03 (br s, 1H), 1.33 and 1.28 (d, *J*=6.57 Hz and 7.05 Hz, total 3H). MS (EI) *m*/*z* 237.
   3b: oil; $[\alpha]_D^{22}$ −9.4 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.31 (d, *J*=3.5 Hz, 1H), 5.20–5.10 (m, 3H), 4.96 (d, *J*=3.6 Hz, 1H), 3.97 (br s, 1H), 2.97 (br s, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 1.32 (m, 1H), 0.92 (br s, 6H). MS (EI) *m*/*z* 279.
   3c: oil; $[\alpha]_D^{22}$ −23.8 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.45 (d, *J*=3.1 Hz, 1H), 5.20–5.10 (m, 3H), 4.98 (d, *J*=3.5 Hz, 1H), 3.80 (br s, 1H), 2.96 (br s, 1H), 2.06 (m, 1H), 0.98 and 0.94 (d, *J*=6.16 and 6.83 Hz, 6H). MS (EI) *m*/*z* 265.
   3d: oil; $[\alpha]_D^{22}$ −51.6 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (m, 10H), 5.36 (d, *J*=3.1 Hz, 1H), 5.25–5.10 (m, 3H), 4.95 (m, 1H), 4.13 (m, 1H), 3.15 (br s) and 2.78 (s, total 1H), 3.05 (m, 1H), 2.67 (dd, *J*=9.8, 13.7 Hz, 1H). MS (EI) *m*/*z* 313.
   3e: mp 77.0–78.0°C; $[\alpha]_D^{22}$ +9.4 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.10 (m, 10H), 5.45 (d, *J*=2.2 Hz, 1H), 5.35–5.25 (m, 2H), 5.25–5.05 (m, 2H), 4.90 (m, 1H), 3.04 (d, *J*=3.0 Hz, 1H). Anal. calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.97; H, 5.68; N, 4.64.