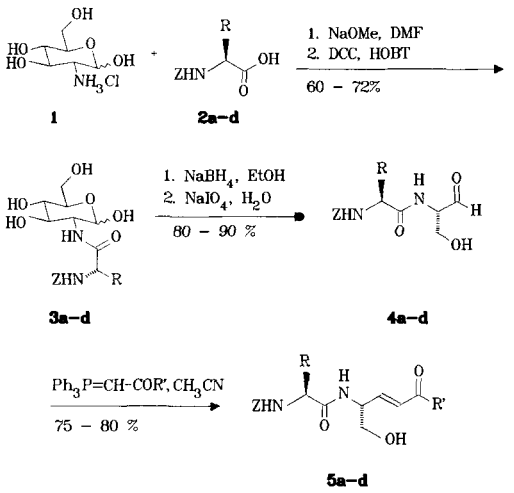
Configuratively Stable Dipeptide Aldehydes from D-Glucosamine Hydrochloride**

By *Thomas Kolter, Annegret Klein,* and *Athanassios Giannis**

Chiral N-protected α-amino aldehydes play an increasingly important role in preparative organic chemistry;[1] however, they are not completely attractive synthetic building blocks because of their chemical and configurative instability.[1] To solve this problem, suitable protecting groups for the amino function have been developed to prevent the racemization of the amino aldehydes during their synthesis, storage, and in subsequent reactions. Rapoport et al.[2] adopted the phenylfluorenyl group, while Reetz et al.[3] studied the *N,N*-dibenzyl function, which in addition leads to notable diastereoselectivity in the addition of organometallic reagents to the protected aminoaldehydes.[3]

With D-glucosamine hydrochloride (**1**)[4] as a chirality-transfer agent, we found an efficient route to *N*-Boc-L-serinal (Boc = *tert*-butoxycarbonyl), a chemically and configuratively stable α-amino aldehyde which can be treated with stabilized phosphorus ylides to provide the corresponding allyl amino alcohols without racemization.[5] This induced us to replace the Boc protecting group with *N*-benzyloxycarbonyl-protected chiral amino acids[6] and thus considerably broaden the synthetic potential of the N-protected serinaldehydes.

Amino aldehydes **4**, with an *N*-benzyloxycarbonylamino acid residue, are available in two steps from D-glucosamine hydrochloride in gram amounts (Scheme 1). These are crystalline substances that can be stored at room temperature and are chemically and configuratively stable. We attribute the unusual stability of these compounds to their oligomeric structure;[7] because of the formation of an intramolecular hemiaminal and an intermolecular hemiacetal, the α H atom has considerably reduced acidity. Thus, in the complex ^{1}H NMR spectra of compounds **4** only a weak (<0.1 H) signal is seen in the range of aldehyde protons. The configuration of the chiral center, the α C atom, was retained under the conditions of the Wittig reaction with stabilized phosphorus ylides. The amino aldehydes **4** were treated with a twofold excess of the phosphorus ylide in refluxing acetonitrile. The resulting Wittig products **5** with *E*-configured double bonds were isolated in 75–80% yield and provided simple ^{1}H NMR spectra.



Scheme 1. Synthesis of the configuratively stable dipeptide aldehydes **4a–d** and peptide Michael acceptors **5** from D-glucosamine hydrochloride **1** and protected amino acids **2a–d**. Z = CO_2CH_2Ph, DCC = dicyclohexylcarbodiimide, HOBT = *N*-hydroxybenzotriazole, DMF = *N,N*-dimethylformamide. **a**: R = *i*Pr, **b**: R = CH_2*i*Pr, **c**: R = CH_2Ph, **d**: R = Me, **5a**: R = *i*Pr, R' = O*t*Bu, **b**: R = CH_2*i*Pr, R' = O*t*Bu, **c**: R = CH_2Ph, R' = O*t*Bu, **d**: R = *i*Pr, R' = Me.

Because these α-amino aldehydes with the *N*-benzyloxycarbonyl-protected amino acid residue can also be considered as dipeptide aldehydes with defined stereochemistry, the method described here provides a new route to peptide aldehydes. The first isolation of naturally occurring peptide aldehydes was conducted by Umezawa, and they are of great pharmacological interest as protease inhibitors.[8]

Compounds related to the peptide Michael acceptor **5** have been described as novel irreversible inhibitors of thiolproteases.[9]

Experimental Procedure

All new compound were characterized by ^{1}H NMR spectroscopy, (high-resolution) mass spectrometry, and elemental analysis. Representative procedures are given.

3a: A solution of **1** (4.32 g, 20 mmol) in DMF (80–100 mL) cooled to 0 °C was treated with sodium methoxide (1.08 g, 20 mmol). The mixture was stirred for 10 min at 0 °C, then **2a** (5.02 g, 20 mmol), hydroxybenzotriazole (5.40 g, 40 mmol), and finally dicyclohexylcarbodiimide (4.54 g, 22 mmoL) were added. After the reaction mixture had been stirred for 1 h, the cooling bath was removed and the mixture stirred another 24 h at room temperature. The precipitate was then removed by filtration, the filtrate treated with diethyl ether (800 mL), and the resulting mixture stored in a refrigerator. The crystalline product that formed was filtered off, and a further crop could be obtained when the filtrate was diluted with diethyl ether. The crude product was recrystallized from ethanol. Yield: 5.90 g (71.5%) **3a**.

M.p. 215 °C (decomp). R_f (dichloromethane: methanol = 4:1) = 0.74. Anomeric ratio $\alpha:\beta = 1:4$. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 0.82 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 1.93 (m, 1H), 3.00–3.70 (m, 7H), 3.85–4.02 (m, 1H), 4.38–5.10 (m, 6H), 6.48 (d, J = 4.7 Hz, 0.2H), 6.55 (d, J = 6.0 Hz, 0.8H), 7.08 (d, J = 9 Hz, 0.2H), 7.17 (d, J = 9 Hz, 0.8H), 7.24–7.40 (m, 5H), 7.65 (d, J = 7.8 Hz, 0.8H), 7.83 (d, J = 7.8 Hz, 0.2H). Correct C,H,N analysis for **3a**. 0.5 H_2O.

4a: Glucosamine derivative **3a** (4.12 g, 10 mmol) was dissolved in ethanol (250 mL) and treated with sodium borohydride (0.57 g, 15 mmol). After the reaction was complete (monitored by TLC), the reaction mixture was filtered through celite and the volatiles were removed by distillation. The residue was taken up in water (250 mL), neutralized with 2 N sulfuric acid, and the resulting solution of the polyol with treated with a solution of sodium periodate (6.42 g in 100 mL water, 30 mmol). When starting material could no longer be detected by TLC (dichloromethane: methanol = 4:1), the reaction mixture was extracted with dichloromethane (4 × 100 mL). The collected organic layers were dried over magnesium sulfate and the solvent removed under reduced pressure. The aldehyde was obtained as a white solid. Yield: 2.7 g (8.37 mmol, 83.7%) **4a**.

M.p. 150 °C. $[\alpha]_D$ +16.8(c = 1.1, DMSO). R_F (CH_2Cl_2/MeOH = 10:1) = 0.44, 0.53. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82–1.08 (m, 6H), 1.95–2.20 (m, 1H), 3.35–4.40 (m, 4H), 4.55–5.95 (m, 4H), 6.90–8.00 (m, 6.9H), 9.55–9.65 (m, 0.1H). Correct C,H,N analysis for **4a** · H_2O. MS (70 eV): $C_{16}H_{22}N_2O_5$ (M^+) calcd.: m/z 322.1529, found: m/z 322.1528: IR: $\tilde{\nu}$ [cm^{-1}] = 3400 (s, shoulder), 3300(s), 3.080(w), 3060(w), 3020(w), 2950(s), 2920(m), 2860(w), 1700(s), 1650(s), 1520(s), 1250(s), 1090(s), 1030(s), 750(m), 700(s).

5a: Aldehyde **4a** (1 equiv) was dissolved in acetonitrile (3 mmol in 50 mL), and after the addition of *tert*-butoxycarbonylmethylenetriphenylphosphorane (2 equiv) the mixture was heated at reflux for 4 h. The reaction mixture was then neutralized with the calculated amount of acetic acid, the solvent removed by distillation, and the remaining oily residue chromatographed on silica gel eluting with hexane:acetone (2:1). Compound **5a** was obtained as a white solid. Preparation: 1.0 g (3.1 mmol) **4a**, yield: 1.0 g (2.38 mmol, 76.8%) **5a**.

M.p. 120–122 °C. $[\alpha]_D$ −16.4 (c = 0.5, $CHCl_3$), R_F (hexane:acetone = 2:1) = 0.32.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, 6.8 Hz, 3H; CH_3), 0.97 (d, 6.8 Hz, 3H; CH_3), 1.45 (s, 9H; $(CH_3)_3$), 2.09 (m, 1H; 3'-CH), 2.99 (t, 6.0 Hz, 1H; OH), 3.63 (m, 1H; 5-H_A), 3.71 (m, 1H; 5-H_B), 4.01 (dd, 8.4 Hz, 6.6 Hz, 1H; 2'-H),

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4.71 (m, 1H; 4-H), 5.01 (d, 12.0 Hz, 1H; benzyl-H_A), 5.10 (d, 12.0 Hz, 1H; benzyl-H_B), 5.57 (d, 8.4 Hz, 1H; NH), 5.90 (d, 16.0 Hz, 1H; 2-H), 6.77 (dd, 16.0 Hz, 5.2 Hz, 1H; 3-H), 6.83 (d, 8.0 Hz, 1H; NH), 7.28–7.38 (m, 5H; aryl-H). Correct C,H,N analysis. MS (70 eV): $C_{22}H_{32}N_2O_6$ (M^+) calcd.: *m/z* 420.2260, found: *m/z* 420.2258. IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3410(m), 3280(s), 3060(w), 3010(w), 2960(m), 2920(m), 2860(w), 1710(s), 1650(s), 1530(s), 1240(s), 1150(s), 1035(s), 750(w), 700(m).

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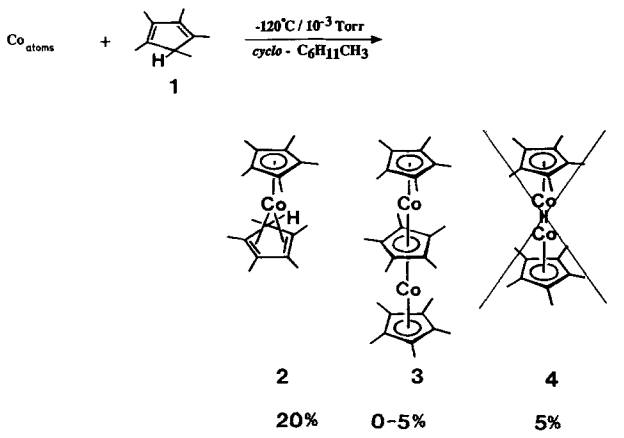
CORRIGENDUM

On the Reaction of Pentamethylcyclopentadiene with Cobalt Atoms: A Reexamination**

By *Jörg J. Schneider**

Over a year ago we reported in this journal the reaction of pentamethylcyclopentadiene Cp*H (**1**) with cobalt atoms.[1] We described the formation of the mononuclear η^4-η^5-sandwich complex **2**, as well as the two Co_2 compounds **3** and "[Cp*Co=CoCp*]" (**4**).[1] Theoretical studies by Abrahamson et al.[2] and preparative work by Theopold et al.[3] prompted us to investigate the title reaction anew. Our former interpretation of the identity of **4** is corrected here.

We succeeded in separating **2** from the multinuclear reaction products **3** and **4** by chromatography and could isolate them as crystals from the eluate by repeated crystallization.[1] A reexamination by mass spectrometry (15 eV, high resolution) of single crystals of **4** yielded a base peak at *m/z* 391.12427 (calculated for $[Cp^*_2Co_2H_3]$ **5**: 391.12461). The ^{1}H NMR study of solutions of these single crystals shows a signal at $\delta_{para} = 29$ (CH_3 on Cp*). More recent MS and ^{1}H NMR investigations of crystals from the mother liquor of **3** and **4** gave a base signal of *m/z* 586 (10 eV, calculated for $[Cp^*_3Co_3H_4]$ **6**: 586.52) and a ^{1}H NMR signal at $\delta_{para} = 61$ (CH_3 on Cp*). This signal had been incorrectly assigned to **6** previously.[1] Because of the almost identical composition, the elemental analyses in general could not distinguish between **4** (now **5**) and **6**. Our initial MS studies of the crude



materials (standard conditions, 70 eV) also gave no evidence of the presence of different compounds with *m/z* 391 and 586.[1]

In conclusion, $[Cp^*_2Co_2]$ (**4**) remains unknown. The compound we described as $[Cp^*_2Co_2]$ is, in fact, $[Cp^*_2Co_2H_3]$ (**5**). $[Cp^*_3Co_3H_4]$ (**6**) is the major component in the eluate of the chromatography after separation of **2** (yield of **6**: 10%), but we formerly did not recognize this.[4]

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[4] We shall soon report on our studies of reactions of cobalt atoms with substituted cyclopentadienes.