Synthesis of Iminodiacetaldehyde Derivatives as Building Blocks for Pharmacologically Active Agents

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Received 8 September 2009; revised 9 November 2009

Abstract: The preparation of iminodiacetaldehyde derivatives is reported via oxidative cleavage of 3,4-dihydroxypyrrolidines with sodium periodate. High yields of iminodiacetaldehydes are obtained starting from *N*-acyl-protected pyrrolidines, whereas the basic *N*-benzyl-protected derivative does not yield the expected dialdehyde. A *cis*-configured dihydroxypyrrolidine, prepared from 2,5-dihydropyrrole, reacts considerably faster with sodium periodate than the corresponding *trans*-configured derivatives which are obtained in three steps from (*R*,*R*)-tartaric acid.

Key words: amino aldehydes, diol, cleavage, oxidation

This paper describes the synthesis of iminodiacetaldehyde derivatives **1** containing various residues at the nitrogen atom. The dialdehydes **1** represent promising building blocks for the synthesis of N-heterocyclic diols **2** of varying ring size (n = 1, 2, 3) (Figure 1).

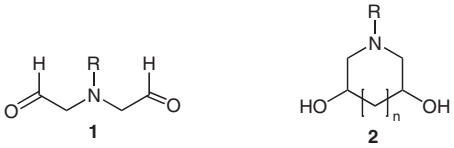
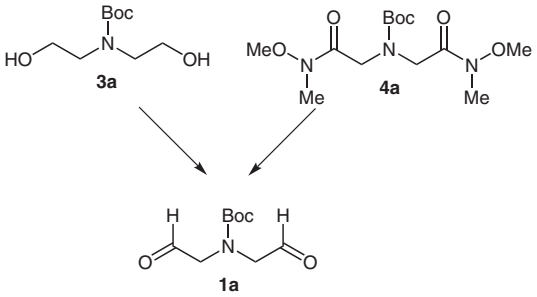


Figure 1 General structures of dialdehydes **1** and N-heterocyclic diols **2**

Compounds containing N-heterocyclic diol units such as **2** exhibit interesting pharmacological properties and multi-step procedures starting from natural products have been reported for their preparation. One such example is the synthesis of polyhydroxylated azepanes, which are potent inhibitors of glucosidases, starting from quinic acid.[1] The reaction of dialdehydes **1** with symmetrical dinucleophiles such as diethyl malonate, diethyl succinate or dimethyl acetone-1,3-dicarboxylate should lead to six-, seven- or eight-membered N-heterocycles, respectively, with potentially interesting pharmacological activity.

For the synthesis of N-heterocyclic diols of type **2**, a reliable method for the preparation of iminodiacetaldehyde derivatives **1** is required. In 1986, Garrigues and Lazraq described two methods for the synthesis of iminodiacetaldehyde **1a** (Scheme 1).[2] According to the first method, Boc-protected iminodiacetaldehyde **1a** was obtained in 65% yield by oxidation of dihydroxy amine **3a** with the Collins reagent [$CrO_3(pyr)_2$]. In the second method, Boc-protected Weinreb amide **4a** was reduced with lithium aluminum hydride to afford **1a** in 56% yield. However, neither a detailed reaction procedure nor a work-up were reported in this short communication,[2] and only limited spectroscopic data were provided.



Scheme 1 Reported syntheses of iminodiacetaldehyde **1a**

Initially, we repeated the reported syntheses. Oxidation of the Boc-protected diol **3a** with the Collins reagent[2] led to the formation of dialdehyde **1a**, as indicated by thin layer chromatography. However, it was not possible to separate dialdehyde **1a** from the accompanying chromium salts. Modification of the reaction conditions and the work-up procedure did not lead to the isolation of the desired product. Therefore, other oxidizing agents were investigated for the oxidation of diol **3a**. The chromium(VI) reagent pyridinium dichromate (PDC),[3] and the hypervalent iodine reagents, iodoxybenzene (IBX)[4] and Dess–Martin periodinane,[5] did not provide the desired dialdehyde **1a**. Swern oxidation[6]of **3a** with oxalyl chloride and dimethyl sulfoxide at –78 °C gave low yields (15–20%) of the desired dialdehyde **1a**. However, purification of **1a** proved to be difficult; rapid hydration and decomposition were observed during flash chromatography on silica gel.

Next, reduction of the Weinreb amide **4a** was investigated. Compound **4a** was prepared by condensation of *N*-Boc-protected iminodiacetic acid and *N*,*O*-dimethylhydroxylamine in the presence of diethyl dicarbonate as the coupling agent.[2] The required Weinreb amide **4a** was isolated in a moderate 41% yield as a result of the formation of several side products. After reduction of **4a** with lithium aluminum hydride, the dialdehyde **1a**, could not be isolated as during the work-up, its separation from aluminum salts proved to be problematic.

SYNTHESIS 2010, No. 5, pp 0791–0796
Advanced online publication: 08.01.2010
DOI: 10.1055/s-0029-1218622; Art ID: T17509SS
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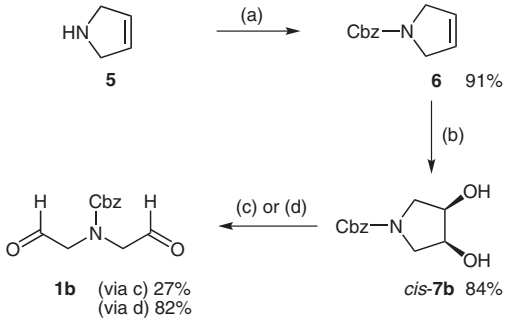
Oxidative cleavage of 3,4-dihydroxypyrrolidines **7** was envisaged as an alternative strategy to obtain dialdehydes **1** in high yields without laborious purification procedures (Scheme 2). Thus, *cis*-configured 3,4-dihydroxypyrrolidine, *cis*-**7b**, was synthesized by acylation of 2,5-dihydropyrrole (**5**) with benzyl chloroformate (CbzCl) and subsequent oxidation of the double bond of intermediate **6** with osmium tetroxide (OsO_4) and *N*-methylmorpholine *N*-oxide (NMO), in an overall yield of 76% (Scheme 2).[7]

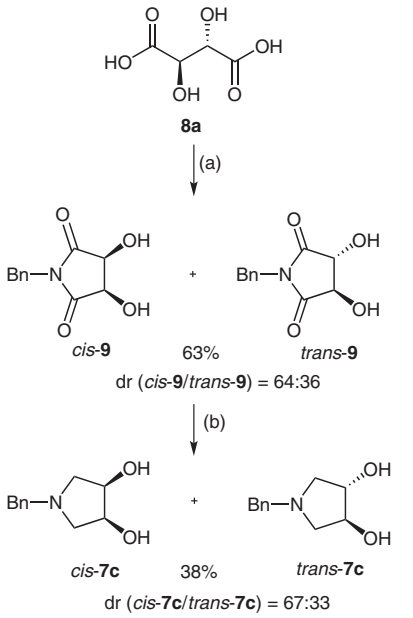


Scheme 2 Synthesis and oxidative cleavage of 3,4-dihydroxypyrrolidine *cis*-**7b**. *Reagents and conditions*: (a) CbzCl, Et_3N, CH_2Cl_2, 24 h; (b) OsO_4, *t*-BuOH, NMO, THF, r.t., 6 h; (c) $Pb(OAc)_4$, CH_2Cl_2, r.t., 3 h; (d) $NaIO_4$, THF, H_2O, r.t., 5 min.

Two common reagents for oxidative cleavage of diols are lead(IV) acetate [$Pb(OAc)_4$][8] in anhydrous solvents, and sodium periodate ($NaIO_4$) in aqueous solution.[9] In order to avoid the formation of aldehyde hydrates the oxidative cleavage of *cis*-**7b** was investigated first with lead(IV) acetate providing dialdehyde **1b** in 27% yield. Since this yield was not satisfactory, cleavage of *cis*-**7b** was performed with sodium periodate in aqueous solution. After a reaction time of five minutes, the transformation was complete and dialdehyde **1b** was isolated in 82% yield. The high yield of **1b** was obtained by careful drying of the dialdehyde solution with magnesium sulfate in order to shift the equilibrium between the dialdehyde and its hydrates (e.g. **10b** or **12b**, cf. Scheme 6) in favor of the dialdehyde.

Having successfully generated dialdehyde **1b**, an improvement of the preparation of 3,4-dihydroxypyrrolidines **7** was investigated. The major drawbacks in the synthesis of the diol *cis*-**7b** are the expensive and unstable starting compound dihydropyrrole (**5**), as well as the high toxicity of osmium tetroxide. The synthesis of *trans*-configured 3,4-dihydroxypyrrolidines starting from (*R*,*R*)-tartaric acid (**8b**) has been reported.[10] Hence, to obtain the *cis*-configured diol *cis*-**7c**, this synthesis was transferred to *meso*-tartaric acid (**8a**) (Scheme 3).

Unexpectedly, condensation of *meso*-tartaric acid (**8a**) with benzylamine resulted in a mixture of diastereomeric diols, *cis*-**9** and *trans*-**9**, in the ratio 64:36. It is thought that, at high temperature (160 °C, 7 h), the basic benzylamine is responsible for the epimerization to the thermodynamically more stable diastereomer, *trans*-**9**. Reduction of the diastereomeric mixture of *cis*-**9**/*trans*-**9** with lithium aluminum hydride gave the 3,4-dihydroxypyrrolidines *cis*-**7c** and *trans*-**7c** in the ratio 67:33. Since separation of the diastereomeric mixtures of pyrrolidines **7** and **9** was not possible by recrystallization or by column chromatography on silica gel, this synthetic route was not pursued any further.



Scheme 3 Synthesis of 3,4-dihydroxypyrrolidines starting from *meso*-tartaric acid. *Reagents and conditions*: (a) $BnNH_2$, *o*-xylene, reflux, 7 h; (b) $LiAlH_4$, THF, reflux, 24 h.

Since it is known that *trans*-configured diols can be cleaved by sodium periodate, although longer reaction times are required,[11] the oxidative cleavage of *trans*-configured pyrrolidine-3,4-diols was investigated. The *trans*-configured diol, *trans*-**7c**, was obtained by condensation of (*R*,*R*)-tartaric acid (**8b**) with benzylamine and subsequent reduction with lithium aluminum hydride.[10] During this transformation *trans*/*cis* epimerization was not observed. The *N*-acyl derivatives, *trans*-**7a** and *trans*-**7d**, were obtained in 92% and 49% yields, respectively, by hydrogenolytic removal of the *N*-benzyl protecting group of *trans*-**7c** and acylation of the resulting secondary amine (Scheme 4).

Following preparation of the *trans*-diols **7** the oxidative cleavage with sodium periodate was carried out (Scheme 5) in a similar manner to that described for *cis*-**7b**. Oxidative cleavage of the Boc- and Bz-protected diols, *trans*-**7a** and *trans*-**7d**, with sodium periodate was complete in 24 hours. Following careful drying of the solutions with magnesium sulfate, the dialdehydes **1a** and **1d** were isolated in 88% and 77% yield, respectively. The *N*-Bn-protected diol *trans*-**7c** reacted immediately with sodium periodate, however, dialdehyde **1c** was not isolated due to the rapid formation of several side products. It is assumed that the tertiary amine group of *trans*-**7c** is responsible for its rapid decomposition.

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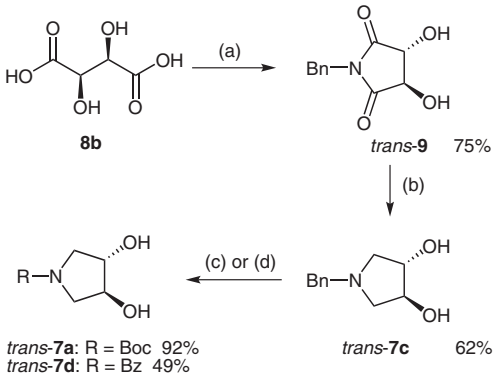
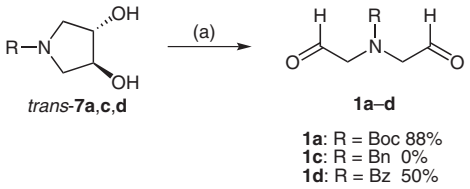


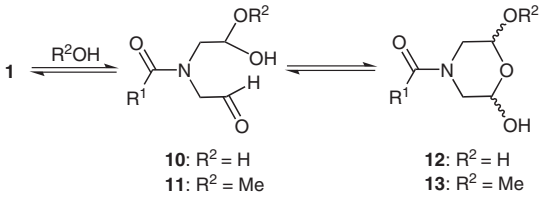
Scheme 4 Synthesis of *trans*-3,4-dihydroxypyrrolidines **7**. *Reagents and conditions*: (a) $BnNH_2$, *o*-xylene, reflux, 20 h; (b) $LiAlH_4$, THF, reflux, 48 h; (c) H_2, Pd/C, Boc_2O, EtOH, r.t., 20 h (*trans*-**7a**); (d) (1) H_2, Pd/C, MeOH, r.t., 20 h; (2) BzCl, K_2CO_3, $CHCl_3$–MeOH (1:1), 0 °C, 20 h (*trans*-**7d**).



Scheme 5 Oxidative cleavage of *trans*-3,4-dihydroxypyrrolidines **7**. *Reagents and conditions*: (a) $NaIO_4$, THF, H_2O, r.t., 24 h.

In general, the oxidative cleavage of *cis*- and *trans*-configured 3,4-dihydroxypyrrolidines **7** with sodium periodate represents an efficient and reliable method for the synthesis of iminodiacetaldehydes **1**. The configuration of the diols **7** had a significant influence on the reaction rate. Whereas cleavage of the *cis*-configured diol *cis*-**7b** was complete after five minutes, the corresponding reaction of *trans*-**7a** and *trans*-**7d** required 24 hours. This difference in reaction rates is based on the relative orientation of the two adjacent hydroxy moieties.

Due to their high reactivity, spectroscopic characterization and determination of the purity of the iminodiacetaldehydes **1** turned out to be very difficult. The ^1H NMR spectrum of **1a**, recorded directly after purification and drying of the sample, is shown in Figure 2. The presence of small amounts of water or alcohols led to the rapid formation of acyclic and cyclic hydrates **10** and **12**, or hemiacetals **11** and **13**, in addition to other products (Scheme 6).



Scheme 6 Formation of hydrates and hemiacetals

In the ^{13}C NMR spectra of **1** weak signals due to the acetal carbon atoms of hydrates **10** and **12** were present in the range 80–90 ppm. The mass spectrum of a sample of **1d** which had been dissolved in methanol, showed, in addition to the mass ion of **1d** (*m*/*z* = 205), peaks for the hydrates **10d/12d** (R^1 = Ph, R^2 = H, *m*/*z* = 246 [M + Na + H_2O]$^+$) and the hemiacetals **11d/13d** (R^1 = Ph, R^2 = Me, *m*/*z* = 260 [M + Na + MeOH]$^+$).

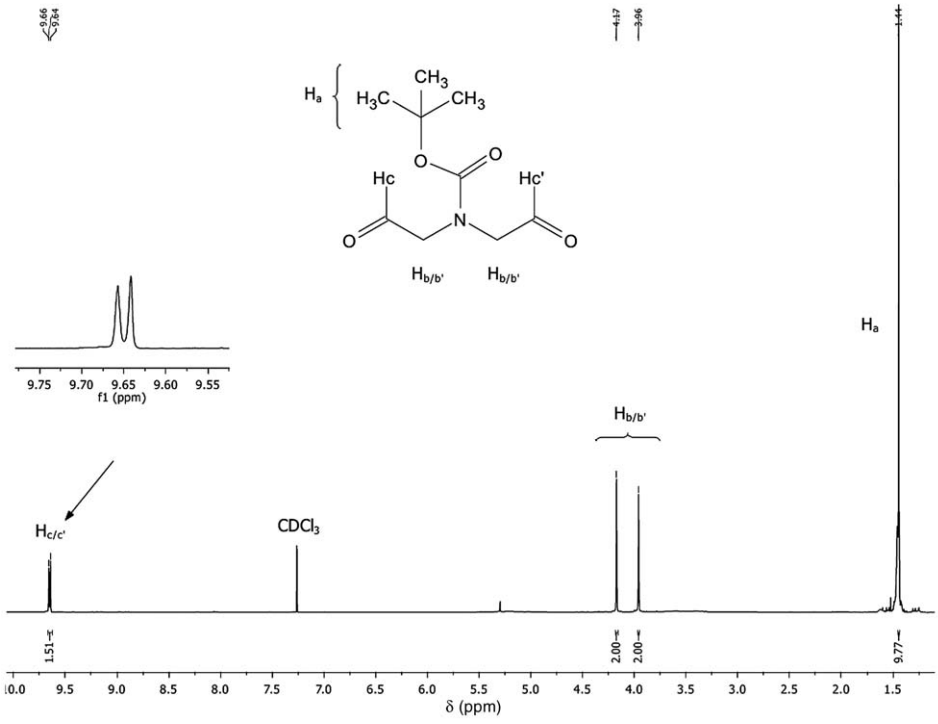


Figure 2 ^1H NMR spectrum of **1a**

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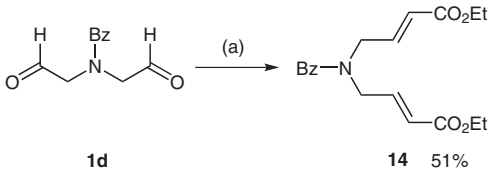
To demonstrate the suitability of the very reactive dialdehyde **1d** in further chemistry, a Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane was carried out (Scheme 7). The resulting diene **14** was obtained in 51% yield. The yield of **14** could be improved via in situ preparation of the dialdehyde **1d** and using it directly without purification in the Wittig reaction.



1d **14** 51%

Scheme 7 Wittig reaction of iminodiacetaldehyde **1d**. *Reagents and conditions*: (a) Ph_3PCHCO_2Et, THF, r.t., 20 h.

In conclusion, an efficient and reproducible method for the synthesis of N-protected iminodiacetaldehyde derivatives **1** has been presented. Various methods for the oxidation of diol **3a** as well as lithium aluminum hydride reduction of the Weinreb amide **4a** did not provide the dialdehyde **1a**. High yields of dialdehydes **1a**, **1b** and **1d** were obtained by oxidative cleavage of the corresponding 3,4-dihydroxypyrrolidines **7** using sodium periodate, provided that the basic nature of the N-atom was negated by the introduction of an *N*-acyl moiety. Whereas the *cis*-configured diol *cis*-**7b** was cleaved within five minutes, the cleavage of the *trans*-configured diols *trans*-**7a** and *trans*-**7d** required 24 hours. The diol *cis*-**7b** was prepared from expensive and unstable 2,5-dihydropyrrole (**5**) using osmium tetroxide as the oxidant. Condensation of (*R*,*R*)-tartaric acid (**8b**) with benzylamine, lithium aluminum hydride reduction and exchange of the N-protecting group gave the *trans*-configured diols, *trans*-**7a** and *trans*-**7d**.

Unless otherwise noted, moisture-sensitive reactions were conducted under anhyd N_2. CH_2Cl_2 and MeOH were distilled over CaH_2. THF was dried over Na/benzophenone and was freshly distilled before use. Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} plates (Merck). Flash chromatography was performed using silica gel 60, 40–64 m (Merck) with the eluent specified in each case. Melting points were recorded using an SMP 3 apparatus (Stuart Scientific) and are uncorrected. HPLC data were obtained using Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 m); LiChroCART® 250–4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm. Method 1: the mobile phase was composed of (A) 100% H_2O and (B) 100% MeCN. TFA (0.05%) was added to both components. The following gradient was applied (A%): 0 min (90%), 4 min (90%), 29 min (0%), 31 min (0%), 31.5 min (90%), 40 min (90%). Method 2: the mobile phase was composed of (A) 100% H_2O and (B) 100% MeOH. TFA (0.05%) was added to both components. The following gradient was applied (A%): 0 min (80%), 1 min (80%), 22 min (0%), 30 min (0%), 31.5 min (80%), 40 min (80%). IR spectra were recorded on a 480 Plus FT-ATR-IR (Jasco) spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained using a Mercury-400BB spectrometer (Varian); chemical shifts (δ) are reported in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. MS spectra were recorded using a MAT GCQ (Thermo-Finnigan) apparatus, EI = electron impact, ESI = electrospray ionization. Exact mass spectra were obtained using MicroTof (Bruker Daltronics) or LTQ Orbitap LTQ XL (Thermo-Fisher Scientific) instruments. The characterization data for compounds **6**,[12] *trans*-**7a**,[13] *trans*-**7c**,[10] *trans*-**7d**[13] and *trans*-**9**[10] was comparable with reported data.

Iminodiacetaldehydes 1; General Procedure

A soln of $NaIO_4$ (1.2 or 1.5 equiv) in H_2O (1.5 mL) was added to a soln of 3,4-dihydroxypyrrolidine **7** (1 equiv) in THF (3.5 mL). After stirring the reaction mixture for 5 min (*cis*-**7**) or 24 h (*trans*-**7**), the solvent was removed under vacuum. The aq layer was sat. with NaCl and extracted with EtOAc (3 × 2 mL). The combined organic layer was dried (Na_2SO_4), filtered, concd under vacuum and the residue was dissolved in anhyd CH_2Cl_2. Anhyd $MgSO_4$ was added, and after stirring for 24 h at r.t., the suspension was filtered and concd under vacuum.

***N*-(*tert*-Butoxycarbonyl)iminodiacetaldehyde (1a)**

Following the general procedure, oxidative cleavage of *trans*-**7a** (102 mg, 0.50 mmol) with $NaIO_4$ (128 mg, 0.6 mmol) was complete in 24 h.

Colorless oil; yield: 88.6 mg (88%); R_f = 0.39 (CH_2Cl_2–MeOH, 10:1).

IR (film): 2978 (w, CH_2), 1731 (m, C=$O_{aldehyde}$), 1690 (s, C=$O_{carbamate}$) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 3.96 (s, 2 H, NCH_2), 4.17 (s, 2 H, NCH_2), 9.64 (s, 1 H, CHO), 9.66 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 58.4 (NCH_2), 58.5 (NCH_2), 82.2 [$C(CH_3)_3$], 155.3 ($C_{carbamate}$), 198.1 (CHO), 198.5 (CHO).

HRMS–ESI (MeCN): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{15}NO_4Na$: 224.0888; found: 224.0893; *m*/*z* [M + Na + H_2O]$^+$ calcd for $C_9H_{15}NO_4Na{\cdot}H_2O$: 242.0999; found: 242.0994.

***N*-(Benzyloxycarbonyl)iminodiacetaldehyde (1b)**

Following the general procedure, oxidative cleavage of *cis*-**7b** (108 mg, 0.45 mmol) with $NaIO_4$ (146 mg, 0.68 mmol) was complete in 5 min.

Colorless oil; yield: 87.0 mg (82%); R_f = 0.37 (CH_2Cl_2–MeOH, 10:1).

IR (film): 2923 (w, CH_2), 1738 (m, C=$O_{aldehyde}$), 1695 (s, C=$O_{carbamate}$), 735, 696 (s, Ar out of plane) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.10 (s, 2 H, NCH_2), 4.22 (s, 2 H, NCH_2), 5.15 (s, 2 H, $ArCH_2$), 7.29–7.38 (m, 5 H, ArH), 9.62 (s, 1 H, CHO), 9.64 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 58.2 (NCH_2), 58.7 (NCH_2), 68.5 ($ArCH_2N$), 128.3 (C_{Ar}), 128.6 (C_{Ar}), 128.8 (C_{Ar}), 135.8 ($C_{q,Ar}$), 155.9 ($C_{carbamate}$), 197.6 (CHO), 197.7 (CHO).

HRMS–ESI (MeCN): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_4$: 236.0917; found: 236.0911; *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{13}NO_4Na$: 258.0737; found: 258.0730; *m*/*z* [2M + Na]$^+$ calcd for $C_{24}H_{26}N_2O_8Na$: 493.1581; found: 493.1566.

***N*-Benzoyliminodiacetaldehyde (1d)**

Following the general procedure, oxidative cleavage of *trans*-**7d** (170 mg, 0.82 mmol) with $NaIO_4$ (263 mg, 1.23 mmol) was complete in 24 h.

Colorless oil; yield: 83.2 mg (50%); R_f = 0.35 (CH_2Cl_2–MeOH, 10:1).

IR (film): 2925 (w, CH_2), 1724 (m, C=$O_{aldehyde}$), 1615 (s, C=O_{amide}), 789, 699 (s, Ar out of plane) cm^{-1}.

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^{1}H NMR ($CDCl_3$): δ = 4.30 (s, 2 H, NCH_2), 4.33 (s, 2 H, NCH_2), 7.35–7.53 (m, 5 H, ArH), 9.54 (s, 1 H, CHO), 9.72 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 60.9 (2 × NCH_2), 127.3 (C_{Ar}), 128.1 (C_{Ar}), 129.4 (C_{Ar}), 135.0 ($C_{q,Ar}$), 172.5 (ArC=O), 196.4 (CHO), 197.1 (CHO).

HRMS–ESI (MeOH): *m/z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_3$: 206.0812; found: 206.0816; *m/z* [M + Na]$^+$ calcd for $C_{11}H_{11}NO_3Na$: 228.0631; found: 228.0630; *m/z* [M + Na + H_2O]$^+$ calcd for $C_{11}H_{11}NO_3Na{\cdot}H_2O$: 246.0737; found: 246.0736; *m/z* [M + Na + MeOH]$^+$ calcd for $C_{11}H_{11}NO_3Na{\cdot}CH_3OH$: 260.0893; found: 260.0893: *m/z* [2M + Na]$^+$ calcd for $C_{22}H_{22}N_2O_6Na$: 433.1370; found: 433.1379.

Benzyl 2,5-Dihydro-1*H*-pyrrole-1-carboxylate (6)[12]

CbzCl (0.21 mL, 1.5 mmol) in toluene (1 mL) was added to a soln of 2,5-dihydropyrrole (**5**) (0.11 mL, 1.5 mmol, 96%) in CH_2Cl_2 (4 mL). Et_3N (0.28 mL, 1.5 mmol) was added dropwise and the reaction was stirred for 24 h at r.t. The reaction mixture was washed with sat. aq NH_4Cl soln (2 × 10 mL) and brine (10 mL) and the aq layer then extracted with EtOAc (3 × 10 mL). The combined organic layer was dried (Na_2SO_4), concd under vacuum and the residue was purified by flash column chromatography (silica gel, cyclohexane–EtOAc, 4:1).

Colorless oil; yield: 278 mg (91%); R_f = 0.31 (cyclohexane–EtOAc, 2:1); purity (HPLC, method 1): 99%, t_R = 19.1 min.

IR (film): 3033 (w, CH), 2953 (w, CH_2), 1699 (s, C=$O_{carbamate}$), 747, 696 (s, Ar out of plane) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.20 (m, 4 H, 2 × NCH_2), 5.17 (s, 2 H, $ArCH_2$), 5.76 (td, 1 H, ^3J = 6.6 Hz, ^3J = 1.7 Hz, CH), 5.80 (td, 1 H, ^3J = 6.5 Hz, ^3J = 1.7 Hz, CH) 7.29–7.40 (m, 5 H, ArH).

MS (EI): *m/z* = 203 [M]$^+$, 91 [$PhCH_2$]$^+$.

***tert*-Butyl (3*S*,4*S*)-3,4-Dihydroxypyrrolidine-1-carboxylate (*trans*-7a)[13]**

Diol *trans*-**7c** (198 mg, 1.0 mmol) was dissolved in EtOH (7 mL) and Boc_2O (247 mg, 1.1 mmol) and Pd/C (16%, 32.7 mg) were added. The reaction mixture was stirred at r.t. under a H_2 atm (1 bar, balloon) for 20 h and then filtered through Celite®. The solvent was removed under vacuum and the residue purified by recrystallization from EtOAc.

Colorless solid; yield: 191 mg (94%); mp 162.5 °C; purity (HPLC, method 1): 99%, t_R = 14.8 min.

IR (neat): 3386 (m, OH), 3321 (m, OH), 2979 (w, CH_2), 1657 (s, C=$O_{carbamate}$) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 3.10 (dd, 2 H, ^2J = 11.6 Hz, ^3J = 3.0 Hz, NCH_2CHOH), 3.29–3.34 (m, 2 H, NCH_2CHOH), 3.83–3.88 (m, 2 H, 2 × C*H*OH), 5.06 (d, 2 H, 2 × CHO*H*).

MS (ESI): *m/z* = 226 [M + Na]$^+$, 429 [2M + Na]$^+$.

Benzyl *cis*-3,4-Dihydroxypyrrolidine-1-carboxylate (*cis*-7b)[7]

A soln of OsO_4 (1.7 mg, 0.007 mmol) in *t*-BuOH (6 mL) was added to a soln of **6** (156 mg, 0.77 mmol) in THF (2 mL). After addition of NMO (90 mg, 0.77 mmol), the reaction mixture was stirred for 6 h at r.t. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc and washed with sat. aq Na_2SO_3 soln, sat. aq $NaHCO_3$ soln and brine. The organic layer was dried (Na_2SO_4), concd in vacuo and the residue purified by flash column chromatography (silica gel, CH_2Cl_2–MeOH, 20:1). In ref.[7] only the mp and R_f value are given.

Colorless solid; yield: 153 mg (84%); mp 82.1 °C; R_f = 0.32 (CH_2Cl_2–MeOH, 10:1); purity (HPLC, method 1): 99%, t_R = 12.5 min.

IR (neat): 3388 (m, OH), 2947 (w, CH_2), 1670 (s, C=$O_{carbamate}$), 744, 696 (s, Ar out of plane) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.54 (br s, 2 H, 2 × OH), 3.36–3.48 (m, 2 H, NCH_2), 3.62–3.69 (m, 2 H, NCH_2), 4.26 (br s, 2 H, 2 × C*H*OH), 5.12 (s, 2 H, $ArCH_2$), 7.29–7.37 (m, 5 H, ArH).

MS (EI): *m/z* = 237 [M]$^+$, 91 [$PhCH_2$]$^+$.

(3*S*,4*S*)-1-Benzylpyrrolidine-3,4-diol (*trans*-7c)[10]

$LiAlH_4$ (1.7 g, 46 mmol) was suspended in THF (150 mL) and the mixture was cooled to 0 °C in an ice-bath. Next, *trans*-**9** (4.4 g, 20 mmol) was added slowly and the mixture was heated under reflux for 48 h. After cooling to –15 °C, H_2O (1.7 mL), NaOH (2 M, 1.7 mL) and H_2O (5.3 mL) were added dropwise. The soln was stirred for 1 h at –15 °C after which the resulting precipitate was removed by filtration. The precipitate was suspended in THF (50 mL), heated to reflux for a short time, and then filtered. This procedure was repeated three times. The filtrate was concd under vacuum and the residue was purified by recrystallization from EtOAc.

Pale-yellow solid; yield: 2.5 g (64%); mp = 99.3 °C; purity (HPLC, method 2): 98%, t_R = 4.6 min.

IR (neat): 3311 (s, OH), 2921 (w, CH_2), 722 (m, Ar out of plane), 697 (s, Ar out of plane) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.29 (dd, 2 H, ^2J = 9.6 Hz, ^3J = 4.3 Hz, NCH_2CHOH), 2.74 (dd, 2 H, ^2J = 9.5 Hz, ^3J = 5.9 Hz, NCH_2CHOH), 3.46 (d, 1 H, ^2J = 13.0 Hz, $ArCH_2$), 3.58 (d, 1 H, ^2J = 13.0 Hz, $ArCH_2$), 3.80–3.87 (m, 2 H, 2 × C*H*OH), 4.83 (d, 2 H, 2 × OH), 7.19–7.34 (m, 5 H, Ar*H*).

MS (EI): *m/z* = 193 [M]$^+$, 91 [$PhCH_2$]$^+$.

(3*R*,4*S*)-1-Benzylpyrrolidine-3,4-diol (*cis*-7c) and (3*S*,4*S*)-1-Benzylpyrrolidine-3,4-diol (*trans*-7c)

Dione **9** (286 mg, 1.3 mmol, *cis*-**9**/*trans*-**9** = 64:36) was added carefully to a suspension of $LiAlH_4$ (154 mg, 4.1 mmol) in THF (5 mL) at 0 °C. The reaction mixture was heated at reflux for 24 h. After cooling to –15 °C, H_2O (60 L), NaOH (2 M, 60 L) and H_2O (180 L) were added dropwise. The soln was stirred for 1 h at –15 °C after which the resulting precipitate was removed by filtration. The precipitate was suspended in THF (5 mL), heated for a short time, and then filtered. This procedure was repeated three times. The filtrate was concd in vacuo and the residue was purified by flash column chromatography [silica gel, CH_2Cl_2→CH_2Cl_2–MeOH (10:1)→CH_2Cl_2–MeOH (5:1)] to afford the product as a diastereomeric mixture (*cis*-**7c**/*trans*-**7c**, 67:33).

Pale-yellow oil; yield: 94.7 mg (38%); R_f = 0.1 (CH_2Cl_2–MeOH, 2:1).

IR (film): 3336 (s, OH), 2922 (s, CH_2), 2804 (s, CH_2), 751 (m, Ar out of plane), 697 (s, Ar out of plane) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ (67:33 diastereomeric mixture) = 2.28 (dd, 2 × 0.67 H, ^2J = 9.5 Hz, ^3J = 4.9 Hz, NCH_2CHOH), 2.29 (dd, 2 × 0.33 H, ^2J = 9.6 Hz, ^3J = 4.3 Hz, NCH_2CHOH), 2.74 (dd, 2 × 0.33 H, ^2J = 9.5 Hz, ^3J = 5.9 Hz, NCH_2CHOH), 2.81 (dd, 2 × 0.67 H, ^2J = 9.5 Hz, ^3J = 6.2 Hz, NCH_2CHOH), 3.46 (d, 0.33 H, ^2J = 13.0 Hz, $ArCH_2$), 3.54 (s, 2 × 0.67 H, $ArCH_2$), 3.57 (d, 0.33 H, ^2J = 13.0 Hz, $ArCH_2$), 3.80–3.87 (m, 2 × 0.33 H, 2 × C*H*OH), 3.91–3.95 (m, 2 × 0.67 H, 2 × C*H*OH), 4.53 (d, 2 × 0.67 H, 2 × OH), 4.83 (d, 2 × 0.33 H, 2 × OH), 7.19–7.36 (m, 5 × 0.33 H, 5 × 0.67 H, ArH).

MS (EI): *m/z* = 193 [M]$^+$, 91 [$PhCH_2$]$^+$.

(3*S*,4*S*)-1-Benzoylpyrrolidine-3,4-diol (*trans*-7d)[13]

Diol *trans*-**7c** (861 mg, 4.5 mmol) was dissolved in MeOH (15 mL) and Pd/C (15%, 470 mg) was added. After stirring for 20 h under a H_2 atm (1 bar, balloon) the mixture was filtered through Celite®. The solvent was removed under vacuum and the residue was dis-

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solved in $CHCl_3$–MeOH (15 mL, 1:1). K_2CO_3 (5.5 g) was added, the mixture cooled to 0 °C and benzoyl chloride (564 μL, 4.9 mmol) was added dropwise. The reaction mixture was stirred for 20 h at r.t. after which the solvent was removed under reduced pressure and the residue was dissolved in Et_2O (10 mL) and filtered. Following evaporation of the solvent in vacuo, the residue was purified by flash column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1).

Pale-yellow oil; yield: 451 mg (49%); R_f = 0.19 (CH_2Cl_2–MeOH, 9:1); purity (HPLC, method 2): 97%, t_R = 6.13 min.

IR (neat): 3386 (m, OH), 3321 (m, OH), 2979 (w, CH_2), 1657 (s, C=O).

^{1}H NMR (DMSO-d_6): δ = 3.15 (d, 1 H, ^3J = 11.2 Hz, NCH_2CHOH), 3.34 (d, 1 H, ^3J = 12.7 Hz, NCH_2CHOH), 3.67 (td, 2 H, ^3J = 11.4 Hz, ^3J = 3.7 Hz, 2 × C*H*OH), 3.89 (br s, 1 H, NCH_2CHOH), 3.98 (d, 1 H, ^3J = 3.7 Hz, NCH_2CHOH), 5.19 (br s, 2 H, 2 × OH), 7.40–7.55 (m, 5 H, ArH).

MS (EI): *m*/*z* = 206 [M – H]$^+$, 105 [PhC=O]$^+$, 77 [Ph]$^+$.

(3*R*,4*R*)-1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione (*trans*-9)[10]

A suspension of (*R*,*R*)-(+)-tartaric acid (**8b**) (751 mg, 5.0 mmol) and benzylamine (0.55 mL, 5 mmol) in *o*-xylene (50 mL) was heated at reflux in a Dean–Stark apparatus. After 20 h, the reaction mixture was cooled to r.t. and the resulting precipitate was removed by filtration. The product was recrystallized from EtOH.

Pale-yellow solid; yield: 905 mg (82%); mp 196.7 °C; purity (HPLC, method 1): >99%, t_R = 10.1 min.

IR (neat): 3439 (w, OH), 3223 (s, OH), 2928 (m, CH_2), 1705 (s, C=O), 745, 690 (s, Ar out of plane) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 4.38 (d, 2 H, ^3J = 2.4 Hz, 2 × C*H*OH), 4.53 (d, 1 H, ^2J = 15.0 Hz, ArCH_2), 4.57 (d, 1 H, ^2J = 15.0 Hz, ArCH_2), 6.31 (br s, 2 H, 2 × OH), 7.22–7.35 (m, 5 H, ArH).

MS (EI): *m*/*z* = 221 [M]$^+$, 106 [C_7H_8N]$^+$, 91 [$PhCH_2$]$^+$.

(3*R*,4*S*)-1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione (*cis*-9) and (3*R*,4*R*)-1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione (*trans*-9)

Benzylamine (0.44 mL, 4 mmol) was added to a suspension of *meso*-tartaric acid (**8a**) (600 mg, 4.0 mmol) in *o*-xylene (50 mL). After heating for 7 h under reflux in a Dean–Stark apparatus, the reaction mixture was cooled to r.t. The resulting precipitate was filtered, washed with cold acetone and dried under high vacuum. The product was recrystallized from EtOH as a diastereomeric mixture (*cis*-**9**/*trans*-**9**, 64:36).

Colorless solid; yield: 561 mg (63%).

IR (neat): 3310 (m, OH), 2945 (w, CH_2), 1699 (s, C=O), 749, 692 (s, Ar out of plane) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ (64:36 diastereomeric mixture) = 4.38 (d, 2 × 0.36 H, ^3J = 2.4 Hz, 2 × C*H*OH), 4.41 (d, 2 × 0.64 H, ^3J = 5.1 Hz, 2 × C*H*OH), 4.53 (d, 0.36 H, ^2J = 15.0 Hz, ArCH_2), 4.54 (s, 2 × 0.64 H, ArCH_2), 4.57 (d, 0.36 H, ^2J = 15.0 Hz, ArCH_2), 6.02 (d, 2 × 0.64 H, ^3J = 5.1 Hz, 2 × OH), 6.31 (br s, 2 × 0.36 H, 2 × OH), 7.21–7.35 (m, 5 × 0.36 H, 5 × 0.64 H, ArH).

MS (EI): *m*/*z* = 221 [M]$^+$, 91 [$PhCH_2$]$^+$.

Diethyl 4,4′-(benzoylimino)bisbut-2-enoate (14)

(Ethoxycarbonylmethylene)triphenylphosphorane (568 mg, 1.63 mmol) was added to a soln of dialdehyde **1d** (127 mg, 0.62 mmol) in THF (5 mL) and the mixture was stirred for 20 h at r.t. Then H_2O was added, the organic solvent was removed in vacuo and the residual mixture was extracted with EtOAc (3 × 5 mL). The combined organics were dried (Na_2SO_4), filtered, concd under vacuum and the residue purified by flash column chromatography (silica gel, cyclohexane–EtOAc, 2:1).

Colorless resin; yield: 109 mg (51%); R_f = 0.53 (cyclohexane–EtOAc, 1:4); purity (HPLC, method 1): 99%, t_R = 19.03–19.71 min.

IR (film): 2981 (w, C–H), 2940 (w, CH_2), 1714 (s, C=O_{ester}), 1699 (s, C=$O_{carbamate}$) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.30 (t, 6 H, ^3J = 7.1 Hz, 2 × CH_3), 4.02 (br s, 2 H, NCH_2), 4.21 (q, 4 H, ^3J = 7.2 Hz, 2 × C$H_2$$CH_3$), 4.25–4.34 (m, 1 H, NCH_2), 4.44–4.77 (m, 1 H, NCH_2), 5.94 (d, 2 H, ^3J = 15.1 Hz, 2 × CH=C*H*CO_2Et), 6.12–6.36 (m, 0.5 H, C*H*=CHCO_2Et), 6.58–6.73 (m, 1.5 H, C*H*=CHCO_2Et) 7.35–7.48 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 14.4 (2 × CH_2*C*H_3), 45.9, 49.9 (2 × NCH_2), 60.9 (2 × *C*$H_2$$CH_3$), 123.4, 123.7 (2 × CH=*C*HC=O), 126.8 (C_{Ar}), 128.7 (C_{Ar}), 128.9 (C_{Ar}), 130.5 (C_{Ar}), 135.1 ($C_{q,Ar}$), 142.4 (*C*H=CHC=O), 145.2 (*C*H=CHC=O), 165.9 (C=O_{amide}), 172.1 (2 × CH*C*=O_{ester}).

MS (EI): *m*/*z* = 345 [M]$^+$, 240 [M – PhC=O]$^+$, 105 [PhC=O]$^+$, 77 [Ph]$^+$.

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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