# Synthesis of β,β′-Diamino Acids from α-Amino Acid Derived β-Lactams

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**Abstract:** Ring opening of protected 3-aminoalkyl-substituted azetidin-2-ones with O-, N-, or S-nucleophiles led to β,β′-diaminocarboxylic esters, amides, and thioesters, respectively. The reaction outcome is improved by addition of catalytic amounts of sodium azide. Reduction of the β-lactam amide moiety led to diamino alcohols.

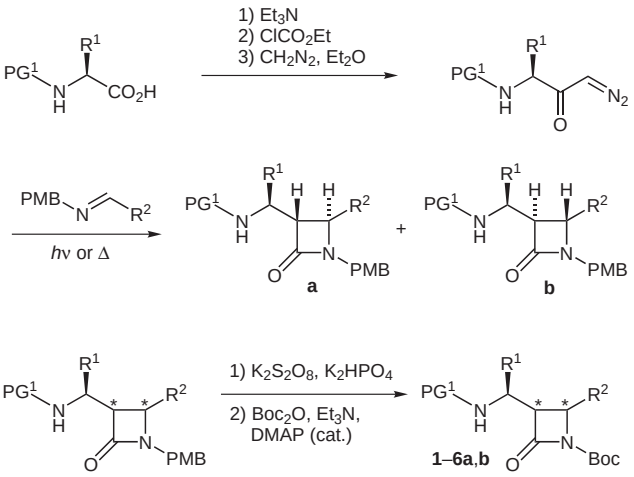
**Key words:** amino acids, chiral pool, diazo compounds, amino alcohols, lactams

β-Lactams are not only part of antibiotics,[1] but are also useful precursors in the preparation of β-amino acids, a class of compounds which found rising attention during the last decades.[2] This has, e.g., been used for synthesis of the side chain in antitumor agent Taxol® (paclitaxel)[3] by nucleophilic ring opening.[4]

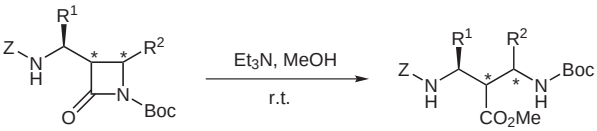
Recently, we presented β-lactam syntheses starting with N-protected α-amino acids, giving rise to aminoalkyl-substituted β-lactams.[5] In this paper we describe a ring opening of these substrates leading to β,β′-diamino acid derivatives. These compounds, though interesting building blocks, have hardly been investigated;[6] a stereoselective synthesis has been reported only once using the ring opening of pyrazolidines.[7] They should be useful as synthetic intermediates, as unnatural amino acids,[8] e.g. for the preparation of peptidomimetics, and, after reduction, as tridentate ligands[9] or therapeutics.[10]

β-Lactam synthesis is simply achieved by photolysis of amino acid derived diazoketones in the presence of imines (Scheme 1).[5] With this method, 4-aryl-substituted β-lactams are accessible while a change to thermal conditions in the decomposition of diazoketones allows the preparation of vinyl- and crotyl-substituted derivatives.[11] With these methods, exclusively *trans*-substituted β-lactams were obtained,[12] where the selectivities are ruled by steric hindrance of the amino acid side chain. They range from 2:1 (alanine, R = Me) to 13:1 (*tert*-leucine, R = *t*-Bu). Starting with L-amino acids the major product is 3*R*,4*S*-configured; the diastereoisomers are simply separated by chromatography.

β-Lactams with an aliphatic substituent or without substituent at the nitrogen are hydrolyzed only under strongly acidic conditions.[13] A mild ring opening is best achieved




**Scheme 1** Synthesis of Boc-protected β-lactams by photochemically or thermally induced Staudinger reaction and subsequent protection-group manipulation




**Scheme 2** Ring opening of β-lactams with methanol

with an electron-withdrawing group at the nitrogen. The *tert*-butyloxycarbonyl (Boc) group is an easy to handle protecting group fulfilling this requirement. *N*-Boc-protected β-lactams **1**–**6** were obtained by oxidative cleavage of the *para*-methoxybenzyl group (PMB) with potassium peroxodisulfate in buffered aqueous acetonitrile at 70 °C and subsequent protection with di-*tert*-butyl dicarbonate ($Boc_2O$).[5b]

While methanolysis of **1a** with sodium methanolate in refluxing methanol led to a poor 33% yield within five hours, the ring opening was achieved with triethylamine in methanol at room temperature giving >97% of the respective β,β′-diamino esters where reaction times had to be extended to about one day.[14] Only substrate **5b** led to a moderate 61% yield caused by a laborious purification procedure (Scheme 2, Table 1). The diamino compounds are N,N′-protected with two different protecting groups allowing for a selective deprotection and utilization in further reactions. No detectable epimerization at any of the stereogenic centers occurred during these and the following reactions.

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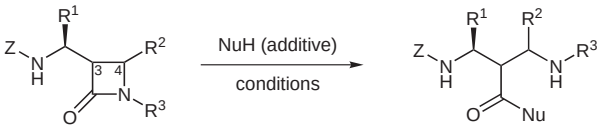
**Table 1** Ring Opening with Methanol

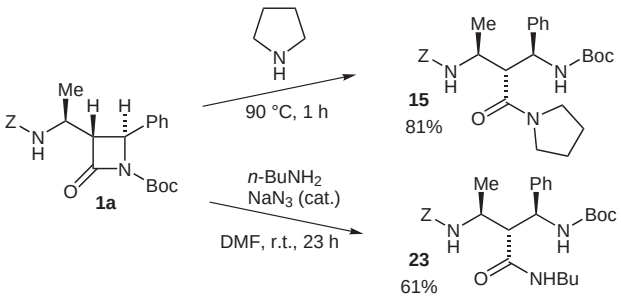
| Entry | β-Lactam | $R^1$ | $R^2$ | Config | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Me | Ph | 3*R*,4*S* | 21 | **10** | 99 |
| 2 | **2a** | Me | 4-$ClC_6H_4$ | 3*R*,4*S* | 24 | **11** | 99 |
| 3 | **3a** | Me | 1,3-dioxolan-2-yl | 3*R*,4*S* | 22 | **12** | 99 |
| 4 | **4a** | *i*-Pr | Ph | 3*R*,4*S* | 16 | **13** | 97 |
| 5 | **5b** | Bn | Ph | 3*S*,4*R* | 24 | **14** | 61 |

**Table 2** Ring Opening with N-, S-, and O-Nucleophiles



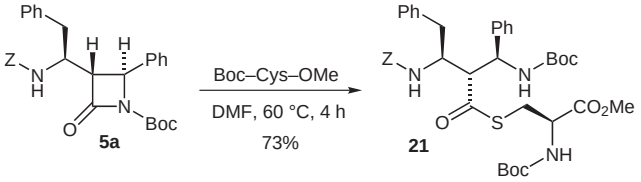

| Entry | β-Lactam | $R^1$ | $R^2$ | $R^3$ | Config | NuH | Additive | Conditions | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Me | Ph | Boc | 3*R*,4*S* | pyrrolidine | – | neat, 90 °C, 1 h | **15** | 81 |
| 2 | **2a** | Me | 4-$ClC_6H_4$ | Boc | 3*R*,4*S* | pyrrolidine | – | neat, 90 °C, 1 h | **16** | 82 |
| 3 | **3a** | *i*-Pr | Ph | Boc | 3*R*,4*S* | morpholine | – | neat, 100 °C, 90 min | **17** | 72 |
| 4 | **6a** | *i*-Pr | 4-$ClC_6H_4$ | Boc | 3*R*,4*S* | morpholine | – | neat, 100 °C, 90 min | **18** | 78 |
| 5 | **1a** | Me | Ph | Boc | 3*R*,4*S* | allyl-SH | – | $Et_3N$, DMF, 60 °C, 4 h | **19** | 79 |
| 6 | **2a** | Me | 4-$ClC_6H_4$ | Boc | 3*R*,4*S* | allyl-SH | – | $Et_3N$, DMF, 60 °C, 4 h | **20** | 70 |
| 7 | **5a** | Bn | Ph | Boc | 3*R*,4*S* | Boc-Cys-OMe | – | $Et_3N$, DMF, 60 °C, 4 h | **21** | 73 |
| 8 | **6a** | *i*-Pr | 4-$ClC_6H_4$ | Boc | 3*R*,4*S* | *t*-BuSH | – | $Et_3N$, DMF, 60 °C, 4 h | **22** | 0 |
| 9 | **6a** | *i*-Pr | 4-$ClC_6H_4$ | Boc | 3*R*,4*S* | *t*-BuSH | $NaN_3$ (cat.) | $Et_3N$, DMF, 60 °C, 24 h | **22** | 68 |
| 10 | **1a** | Me | Ph | Boc | 3*R*,4*S* | *n*-$BuNH_2$ | $NaN_3$ (cat.) | DMF, rt, 23 h | **23** | 61 |
| 11 | **2b** | Me | 4-$ClC_6H_4$ | Boc | 3*S*,4*R* | *n*-$BuNH_2$ | $NaN_3$ (cat.) | DMF, r.t., 42 h | **24** | 79 |
| 12 | **5b** | Bn | Ph | Boc | 3*S*,4*R* | allyl-$NH_2$ | $NaN_3$ (cat.) | DMF, r.t., 24 h | **25** | 61 |
| 13 | **7a** | Me | Ph | H | 3*R*,4*S* | MeOH | $ClSiMe_3$ | MeOH, r.t., 66 h | **26** | 58 |
| 14 | **8b** | Bn | 4-$ClC_6H_4$ | H | 3*S*,4*R* | MeOH | $ClSiMe_3$ | MeOH, r.t., 48 h | **27** | 53 |
| 15 | **9a** | *i*-Pr | 4-$ClC_6H_4$ | H | 3*R*,4*S* | MeOH | $ClSiMe_3$ | MeOH, r.t., 24 h | **28** | 51 |

Ring opening with methanol was similarly, albeit more sluggishly achieved starting with the N-unprotected β-lactams in the presence of chlorotrimethylsilane as Lewis acid according to a protocol of Palomo et al. (Table 2, entries 13–15).[15] Thus obtained unprotected amines could, e.g. for reasons of analysis, be protected with the Boc group using a standard protocol. Nevertheless, they are reasonable stable and crystallized in some cases. No epimerization was observed with these conditions, which could be proven, inter alia, by X-ray crystallographic analysis of amine **27**.[16]

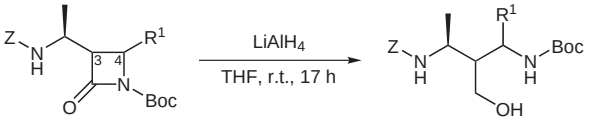



**Scheme 3** Ring opening of β-lactams with N-nucleophiles

Ring opening with secondary amines like pyrrolidine or morpholine was cleanly achieved at elevated temperatures. The respective amides were obtained as analytically pure, crystalline solids in good yields (Scheme 3, Table 2, entries 1–4). Addition of primary amines was very sluggish with these conditions, but was proceeding at ambient temperatures when sodium azide was added as catalyst




**Scheme 4** Ring opening of β-lactams with a cysteine derivative




**1b** → **29**, $R^1$ = Ph, 3*S*,4*R*: 41%

**2a** → **30**, $R^1$ = 4-Cl$C_6H_4$, 3*R*,4*S*: 40%

**Scheme 5** Reductive ring opening of β-lactams

(entries 10–12).[17,18] Again, the stereochemical integrity and the structure of these compounds could be proven by X-ray crystallographic analysis of amides **15** and **17**.[16]

Astonishingly, neither the addition of *N*,*O*-dimethyl- nor of *O*-methylhydroxylamine (liberated from the respective hydrochlorides by addition of triethylamine) was successful, even in the presence of sodium azide.[19] While the former did not react at all, the latter gave traces of a hydroxamic acid within five days. The target products (Weinreb amides) would have been useful for further reaction, e.g. for the preparation of ketones.

The ring opening with thiols[20] leading to thiocarboxylic acids is achieved with high yields in the presence of a base (triethylamine) at slightly elevated temperatures (Table 2, entries 5–7). Addition of N,O-diprotected cystein is possible similarly (Scheme 4) while the addition of the bulky *tert*-butyl thiol proceeded only in the presence of sodium azide as catalyst and with a longer reaction time. With this variation similar yields were obtained as with primary thiols (entry 9).

Reductive ring opening of β-lactams to 1,3-amino alcohols is usually achieved with either lithium aluminium hydride,[21] with sodium borohydride,[22] or with lithium borohydride.[23] We used lithium aluminium hydride as reducing agent for β-lactams **1b** and **2a** and obtained diamino alcohols **29** and **30** after basic workup (Scheme 5).[24]

We presented a method for the simple preparation of β,β′-diaminocarboxylic esters, amides, and thioesters and of diamino alcohols starting with α-amino acids. Evaluation of scope and limitations of this approach and its utilization in the synthesis of peptidomimetics is currently in progress in our laboratories.

## Acknowledgment

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(14) **Methyl (2*R*,3*S*,1′*S*)-3-(Benzyloxycarbonylamino)-2-[(*tert*-butyloxycarbonylamino)phenylmethyl]butanoate (10)**

$Et_3N$ (100 μL, 718 μmol) was added to β-lactam **1a** (102 mg, 240 μmol) in anhyd MeOH (7 mL). After stirring for 21 h at r.t. (TLC) the volatile components were removed at reduced pressure and the remnant was purified by chromatography ($SiO_2$, *n*-hexane–EtOAc, 3:1) yielding methyl ester **10** (109 mg, 239 μmol, 99%) as a colorless wax: $[\alpha]_D^{20}$ –23.0 (*c* 1.05, $CHCl_3$). $^1$H NMR (500 MHz, DMSO-$d_6$): δ = 1.03 (d,

$^3J$ = 6.7 Hz, 3 H, 4-H), 1.35 [s, 9 H, $C(CH_3)_3$], 2.89 (dd, $^3J$ = 8.3 Hz, $^3J$ = 6.7 Hz, 1 H, 2-H), 3.49 (s, 3 H, $OCH_3$), 3.54 (ddq, $^3J$ = 9.1 Hz, $^3J$ = 7.0 Hz, 1 H, 3-H), 4.85 (dd, $^3J$ = 9.6, 8.4 Hz, 1 H, 1′-H), 4.96 (d, $^2J$ = 12.6 Hz, 1 H, $OCH_aH_bPh$), 5.05 (d, $^2J$ = 12.6 Hz, 1 H, $OCH_aH_bPh$), 6.87 (d, $^3J$ = 9.2 Hz, 1 H, NH), 7.13 (d, $^3J$ = 9.9 Hz, 1 H, 2′-H), 7.22–7.39 (m, 10 H, $C_6H_5$). $^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 19.5 (q, C-4), 28.3 [q, $C(CH_3)_3$], 46.5 (d, C-3), 52.0 (q, $OCH_3$), 53.3 (d, C-1′), 56.2 (d, C-2), 66.6 (t, $OCH_2Ph$), 79.8 [s, $C(CH_3)_3$], 126.2, 127.7, 128.1, 128.1, 128.5, 128.7 (6 d, 2 $C_6H_5$), 136.6, 139.9 (2 s, $C_6H_5$ *ipso*), 155.0 (s, $NHCO_2t$-Bu), 155.4 (s, $NHCO_2Bn$), 173.1 (s, C-1). IR (DRIFT): ν =3416, 3337 (NH), 3065, 3033, 2978 (CH), 1722 (C=O), 1604, 1587, 1500 (C=C) $cm^{-1}$. MS (FAB pos.): *m/z* (%) = 479 (3) $[M + Na]^+$, 457 (4) $[M + H]^+$, 357 (89), 282 (10), 178 (26), 163 (15), 106 (17), 91 (100). HRMS (EI): *m/z* calcd for $^{12}C_{25}{}^1H_{33}{}^{14}N_2{}^{16}O_6$: 457.2339; found: 457.2344.

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(18) **(2*S*,3*S*,1′*R*)-3-(Benzyloxycarbonylamino)-*N*-butyl-2-[(*tert*-butyloxycarbonylamino)-4-chlorphenylmethyl]-butanamide** (**24**)
$BuNH_2$ (23 μL, 233 μmol) and $NaN_3$ (2 mg, 31 μmol) were added to a solution of β-lactam **2b** (81 mg, 176 μmol) in anhyd DMF (1 mL) under argon. The mixture was stirred for 42 h at r.t. (TLC), poured into brine (6 mL), and extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by chromatography ($SiO_2$, *n*-hexane–EtOAc, 4:1 → 2:1) yielding **24** (74 mg, 139 μmol, 79%) as a colorless solid: mp 176–178 °C; $[\alpha]_D^{20}$ +3.9 (*c* 1.00, $CHCl_3$). $^1H$ NMR (500 MHz, DMSO-$d_6$): δ = 0.72 (t, $^3J$ = 7.2 Hz, 3 H, $CH_2CH_3$), 0.86 (dtq, $^2J$ = 13.7 Hz, $^3J$ = 7.9, 7.0 Hz, 2 H, $CH_2CH_3$), 0.98 (d, $^3J$ = 6.5 Hz, 3 H, 4-H), 1.05 (dtt, $^2J$ = 13.1 Hz, $^3J$ = 7.8, 6.5 Hz, 2 H, $CH_2CH_2CH_3$), 1.36 [s, 9 H, $C(CH_3)_3$], 2.57 (dd, $^3J$ = 10.9 Hz, $^3J$ = 3.6 Hz, 1 H, 2-H), 2.68 (ddt, $^2J$ = 13.3 Hz, $^3J$ = 6.7, 4.9 Hz, 1 H, $NHCH_aH_b$), 2.94 (ddt, $^2J$ = 13.2 Hz, $^3J$ = 6.6, 5.9 Hz, 1 H, $NHCH_aH_b$), 3.86 (ddq, $^3J$ = 10.8 Hz, $^3J$ = 8.8, 6.5 Hz, 1 H, 3-H), 4.94 (dd, $^3J$ = 8.4, 3.5 Hz, 1 H, 1′-H), 4.98 (d, $^2J$ = 12.4 Hz, 1 H, $OCH_aH_bPh$), 5.02 (d, $^2J$ = 12.5 Hz, 1 H, $OCH_aH_bPh$), 6.95 (d, $^3J$ = 8.4 Hz, 1 H, $NHCO_2t$-Bu), 7.21 (d, $^3J$ = 8.5 Hz, 2 H, $C_6H_4Cl$: 2″-H, 6″-H), 7.30–7.36 (m, 7 H, $C_6H_4Cl$: 3″-H, 5″-H, Ph), 7.49 (d, $^3J$ = 8.8 Hz, 1 H, NH), 7.92 (t, $^3J$ = 5.4 Hz, 1 H, $NHCH_2$). $^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 13.6 (q, $CH_2CH_3$), 18.4 (q, C-4), 19.7 (t, $CH_2CH_3$), 28.4 [q, $C(CH_3)_3$], 31.1 (t, $CH_2CH_2CH_3$), 39.0 (t, $NHCH_2$), 47.4 (d, C-3), 52.6 (d, C-1′), 56.2 (d, C-2), 66.6 (t, $OCH_2Ph$), 79.5 [s, $C(CH_3)_3$], 127.3 (d, $C_6H_4Cl$: C-2″, C-6″), 128.0, 128.1, 128.5 (3 d, Ph), 128.5 (d, $C_6H_4Cl$: C-3″, C-5″), 132.8 (s, $C_6H_4Cl$: C-4″), 136.5 (s, Ph), 140.1 (s, $C_6H_4Cl$: C-1″), 155.5 (s, $NHCO_2t$-Bu), 155.6 (s, $NHCO_2Bn$), 171.3 (s, C-1). IR (DRIFT): ν = 3344 (NH), 3067, 3035, 2966, 2934, 2874 (CH), 1688, 1645 (C=O, amide I), 1537 (NHCO, amide II) $cm^{-1}$. MS (FAB pos.): *m/z* (%) = 554 (30) $[M + Na]^+$, 532 (34) $[M + H]^+$, 476 (24), 432 (100), 238 (77), 180 (12), 165 (15), 140 (12), 91 (79). Anal. Calcd for $C_{28}H_{38}ClN_3O_5$ (532.07): C, 63.21; H, 7.20; N, 7.90. Found: C, 63.24; H, 7.18; N, 8.15.

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