A Mild Multistep Conversion of N-Protected α-Amino Acids into N-Protected β^3-Amino Acids Utilizing the Nef Reaction

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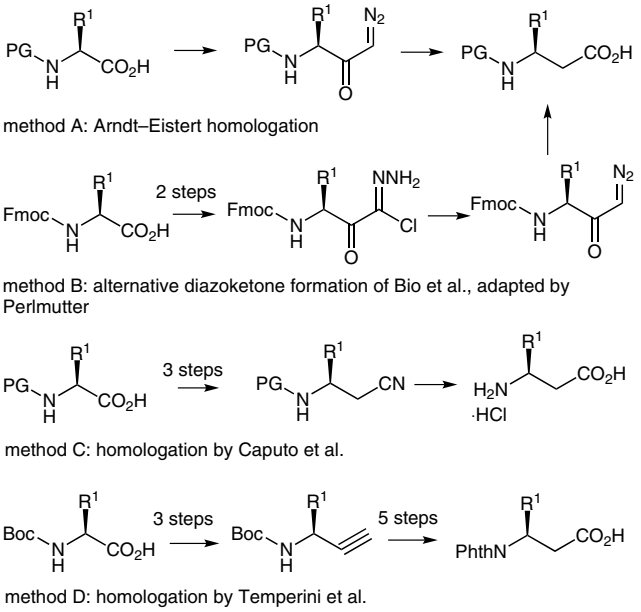
Abstract: Current methods of homologation of α-amino acids to β-amino acids have limitations. To overcome these shortfalls the Nef reaction has been utilized in the multistep synthesis of β^3-amino acids from α-amino acids. In this approach, N-protected amino aldehydes, easily accessed from α-amino acids, were transformed into the N-protected γ-amino nitroalkanes. The Nef reaction was then used to smoothly convert the nitroalkanes into the corresponding N-protected β^3-amino acids without notable racemization.

Key words: amino acids, amino alcohols, amino aldehydes, nucleophilic addition, enantioselectivity

The popularity of applications of β-amino acids as either synthons in organic chemistry or in peptidomimetics in bioorganic and medicinal chemistry is increasing. As a result a plethora of syntheses exist.[1] Of these syntheses a limited number of examples exist for the direct homologation of α-amino acids to β^3-amino acids. The use of a homologation allows the chirality to be transferred to the β^3-amino acid product, and does not have the requirement to use expensive, and sometimes toxic, chiral transfer reagents to install chirality in the final product.

The most well-known procedure to perform the homologation of α-amino acids to β^3-amino acids is the Arndt–Eistert homologation (method A, Scheme 1).[2,3] However, this two-step transformation has limitations in the toxicity and safe generation of diazomethane. As a result many alternative procedures have appeared (Scheme 1). These procedures have advantages and disadvantages. As a result there is still an unmet need to develop a novel strategy that is mild, inexpensive, safe, possesses a limited number of synthetic steps, and transfers the chirality of the α-amino acid to the β^3-amino acid product faithfully. The protocol of Caputo[4] (method C, Scheme 1) has gone a long way to achieving these idealities; however, the method requires the use of cyanide. Further, hydrolysis of the nitrile also results in loss of the N-protective group. An alternative to the use of diazomethane in the Arndt–Eistert homologation is the procedure by Bio et al.[5] that utilizes *N*-isocyano iminotriphenylphosphorane to produce diazoketones in three steps. More recently, this method has been applied to the homologation of *N*-Fmoc α-amino acids by Perlmutter.[6] The limitation of this method is the phosphorane reagent is relatively expensive and an *N*-Fmoc acid chloride is required for the method to be viable (method B, Scheme 1). And finally, Temperini et al.[7] developed a synthetic sequence using inexpensive reagents, via an alkyne to produce β^3-amino acids (method D, Scheme 1). However, eight synthetic steps were required.



Scheme 1 Literature examples of the homologation of α-amino acids to β^3 amino acids. PG = protecting group; R^1 = amino acid side chain.

There are numerous other homologation procedures,[8] however, most are not applicable to β-amino acid synthesis. The methods that are, produce substituted β^2, β^{2,3} or β^{2,2,3}-amino acids,[9] not β^3-amino acids, the focus of the work described here. One such example that produces a hydroxy-substituted β^{2,3}-amino acid is a method that incorporates the use of the Nef reaction (Scheme 2).[10] To the best of our knowledge the Nef reaction has not been used in the production of β^3-amino acids. It is proposed to perform a Henry reaction on an α-amino aldehyde. The hydroxyl group present on the Henry reaction product will then be reductively eliminated, so a Nef reaction can be exploited to enable the synthesis of β^3-amino acids from α-amino acids without racemization (Scheme 2). Preliminary results investigating the use and scope of the Nef re-

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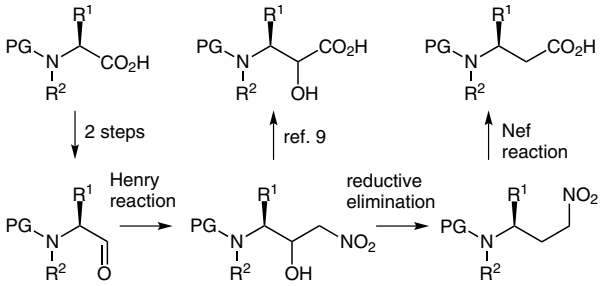
action in the production of β^3-amino acids are described herein.

To demonstrate the scope of the proposed synthetic route, a small number of α-amino acid residues were selected with different side-chain functionalities, N-nonmethylated and N-methylated, and in the presence of a few common N-protecting groups, such as Cbz, Boc, and Ts.

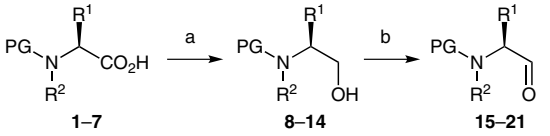


Scheme 2 Study proposed utilising the Nef reaction in the production of β^3-amino acids. PG = protecting group; R^1 = amino acid side chain; R^2 = H, Me.

To enable the exploitation of the Nef reaction, the γ-amino nitroalkane was required as a key synthon. It was proposed this intermediate would be accessed from an elimination of the product obtained from the Henry reaction of nitromethane with the α-amino aldehyde. The amino aldehyde will be accessed via a two-step process from the N-protected α-amino acid (Scheme 2).

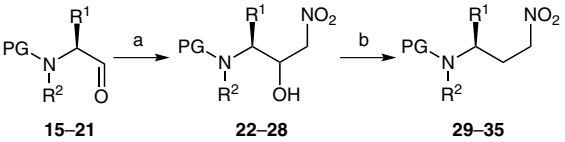
N-Protected amino alcohols **8**–**14** can be obtained using a number of approaches. The approach used involved activating the N-protected α-amino acid **1**–**6** using *N*-methylmorpholine and ethyl chloroformate at –15 °C, followed by the addition of sodium borohydride (Scheme 3).[11] This gave the N-protected amino alcohols **8**–**13** in good to excellent yields (76–86%, Table 1). The *N*-tosyl analogue **7** was converted into the amino alcohol **14** using $LiAlH_4$.

α-Amino aldehydes **15**–**21** can also be obtained by a variety of different methods,[12] however, a Swern oxidation of the amino alcohols **8**–**14** at low temperature was chosen



Scheme 3 Conversion of N-protected α-amino acids into N-protected α-amino aldehydes. *Reagents and conditions*: (a) for **8**–**13**: 1. NMM, EtOCOCl, THF, –15 °C; 2. $NaBH_4$, MeOH, H_2O; for **14**: $LiAlH_4$, THF, reflux, 2 h; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C (for PG, R^1 and R^2 refer to Table 1).

(Scheme 3), in order to minimize racemization.[13] Racemization of α-amino aldehydes can occur at room temperature in a short period, and to minimize racemization they were used immediately in the next transformation. The Swern reaction products **15**–**21** were immediately subjected to a modified Henry reaction, using nitromethane in the presence of potassium fluoride (Scheme 4).[14] The use of potassium fluoride, in place of a strong base usually used in the Henry reaction, also minimized the risk of racemizing the α-amino aldehydes **15**–**21**. The level of racemization was monitored only in the final β^3-amino acid product. The intermediate γ-amino β-hydroxy nitroalkanes **22**–**28** were obtained in mediocre to good yields [37–70% (calculated from the starting amino alcohols **8**–**14**), Table 1].[21] The β-hydroxy nitroalkanes **22**–**28** were obtained as a mixture of diastereoisomers, and thus were not characterized at this stage, but used directly in the next transformation. The diastereoselectivity of the Henry reaction was thus not important as the β-hydroxy stereocenter was removed in the next step.



Scheme 4 Conversion of α-amino aldehydes into γ-amino nitroalkanes. *Reagents and conditions*: (a) $MeNO_2$ (4 equiv), KF (1 equiv), *i*-PrOH, 0–25 °C, 8 h; (b) 1. Ac_2O, cat. DMAP, Et_2O 25 °C, 2 h; 2. $NaBH_4$, EtOH, 0 °C, 2 h (for PG, R^1 and R^2 refer to Table 1).

Table 1 Conversion of N-Protected α-Amino Acids **1**–**7** into Nitroalkanes **29**–**35**

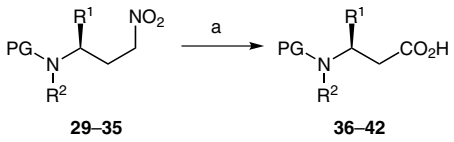
Entry	PG	R^1	R^2	α-Amino acid	Yield of amino alcohol (%)	Amino aldehyde	Yield of β-hydroxynitro alkane (%)[a]	Yield of nitro alkane (%)
1	Cbz	Me	H	**1**	**8** 80	**15**	**22** 63	**29** 70
2	Cbz	Bn	H	**2**	**9** 86	**16**	**23** 60	**30** 53
3	Boc	CH_2OBn	H	**3**	**10** 79	**17**	**24** 40	**31** 48
4	Boc	*i*-Pr	H	**4**	**11** 83	**18**	**25** 60	**32** 65
5	Cbz	Bu	Me	**5**	**12** 86	**19**	**26** 55	**33** 60
6	Cbz	CH_2CO_2Bn	Me	**6**	**13** 82	**20**	**27** 70	**34** 63
7	Ts	*i*-Bu	H	**7**	**14** 76	**21**	**28** 37	**35** 55

[a] Yield calcd from the starting amino alcohol.

Table 2 Conversion of Nitroalkanes **29**–**35** into N-Protected β³-Amino Acids **36**–**42**

Entry	PG	R^1	R^2	Nitro alkane	Yield of product (%)	Found [α] (*c*)	Lit. [α] (*c*, solvent)
1	Cbz	Me	H	**29**	**36** 75	–12.5 (1.04)	–15.7 (1.04, $CHCl_3$)[17]
2	Cbz	Bn	H	**30**	**37** 67	–30.0 (1.0)	–36.0 (1.0, $CHCl_3$)[18]
3	Boc	CH_2OBn	H	**31**	**38** 60	+16.6 (1.05)	+15.1 (1.05, $CHCl_3$)[19]
4	Boc	*i*-Pr	H	**32**	**39** 67	–20.0 (1.0)	–20.3 (1.0, $CHCl_3$)[20]
5	Cbz	Bu	Me	**33**	**40** 69	+6.4 (3.1)	+5.5 (3.1, MeOH)[3]
6	Cbz	CH_2CO_2Bn	Me	**34**	**41** 70	+2.0 (1.0)	+0.7 (1.0, MeOH)[3]
7	Ts	*i*-Bu	H	**35**	**42** 76	–30.5 (2.4)	–12.5 (2.4, CH_2Cl_2)[16]

In a one-pot process the β-hydroxy functionality on nitroalkanes **22**–**28** was reductively eliminated using the conditions of Wollenberg et al.[14] The hydroxy group was first converted into an *O*-acetate, using acetic anhydride and 4-dimethylamino pyridine, and then in the same pot the *O*-acetate was reduced using sodium borohydride (Scheme 4). The one-pot procedure proceeded smoothly giving good yields (48–70%) of the nitroalkanes **29**–**35** (Table 2) after purification by column chromatography.[22]



Scheme 5 Conversion of γ-amino nitroalkanes into β³-amino acids. *Reagents and conditions*: (a) $NaNO_2$ (3 equiv), AcOH (10 equiv), DMSO, 40 °C, 20 h (for PG, R^1 and R^2 refer to Table 2).

The nitroalkanes **29**–**35** were then converted into the β³-amino acids using the Nef reaction carried out using the conditions of Mioskowski et al.[15] These conditions involve the use of three equivalents of sodium nitrite and ten equivalents of acetic acid in DMSO at 40 °C (Scheme 5).[23] These conditions were applied to all residues and produced the β³-amino acids **36**–**42** in good yields (60–70%, Table 2). The enantiomeric purities of the β³-amino acid products **36**–**42** obtained via the multistep sequence were compared to literature optical rotation values (Table 2). The values for compounds **36**–**42** (Table 2, entries 1–6) compared well. However, the *N*-tosyl analogue **42** (Table 2, entry 7) did not compare well with the literature value.[16] The optical rotation value for **42** is significantly higher than that quoted in the literature. To prove unequivocally that **42** was enantiopure, chiral HPLC was performed. The *N*-tosyl analogue **42** possessed 99% enantiomeric excess.

In conclusion, a preliminary study converting α-amino acids via a mild multistep synthesis, utilizing the Nef reaction, into β³-amino acids has been described. To obtain the Nef reaction synthon, γ-amino nitroalkanes **29**–**35**, N-protected α-amino aldehydes **15**–**21** were converted into the β-hydroxy-nitroalkanes **22**–**28** using the Henry reaction. The hydroxyl functionality was then reductively eliminated in a two-step process, to obtain the Nef synthons **29**–**35**. And finally the Nef reaction proceeded smoothly to obtain a small selection of NH- and *N*-methyl N-protected β³-amino acids **36**–**42**. Residues were obtained without racemization of the chiral center. The overall conversion from N-protected α-amino acids into the desired β³-amino acids occurs in five steps. Although the number of synthetic steps used here is greater than earlier methods, this approach only requires the use of inexpensive and nontoxic reagents. Table 3 helps to facilitate comparison of the current work with previous methods. Future studies will focus on shortening the synthetic sequence and improving synthetic yields, to further highlight that the Nef reaction in the production of β³-amino acids is a viable alternative to current homologation methods.

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Table 3 Comparison of Overall Yields for Conversion of α-Amino Acids into β³-Amino Acids

Residues	Homologation Methods			
	Arndt–Eistert	Caputo	Temperini	Current method
Cbz-β³-Ala	72% (2 steps)	40%[24] (5 steps)	–	26%
Cbz-β³-Val	63%[25] (2 steps)	28%[24] (5 steps)	19%[7] (8 steps)	22%
Cbz-β³-Phe	77%[26] (2 steps)	35%[24] (5 steps)	–	20%

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(21) **General Procedure B: Preparation of N-Protected β-Hydroxy Nitroalkanes 22–28**
Oxalyl chloride (9.56 mmol) was dissolved in CH_2Cl_2 (20 mL), the mixture was cooled to –78 °C, and a solution of dry DMSO (19.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise during 15 min. The N-protected amino alcohol **8**–**14** (4.78 mmol) in CH_2Cl_2 (15 mL) was added dropwise during 10 min, the resulting solution was stirred for 10 min at –78 °C, and a solution of Et_3N (28.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise during 15 min. After 20 min, H_2O (5.0 mL) was added to the vigorously stirred solution at –78 °C. The resulting slurry was poured in Et_2O (50 mL) and washed with 20% aq $KHSO_4$ (2 × 30 mL), the layers were separated, and the aqueous layer was back-extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure (at <20 °C) to afford the crude aldehyde **15**–**21**, which was immediately used in the next reaction without any further purification.
To a solution of crude aldehyde **15**–**21** and nitromethane (19.1 mmol, 4 equiv) in *i*-PrOH (30 mL), cooling to 0 °C, was added KF (4.78 mmol, 1 equiv). The reaction mixture was warmed to r.t. and stirred for 8 h, H_2O (50 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was subjected to flash column chromatography, eluting with 10–35% EtOAc–hexane to give a diastereomeric mixture of nitro alcohols **22**–**28**. The diastereomeric mixture of β-hydroxy nitroalkanes **22**–**28** were not characterized and were used directly in the next reaction.

(22) **General Procedure C: Preparation of N-Protected γ-Amino Nitroalkanes 29–35**
To the β-hydroxy nitroalkane **22**–**28** (1.79 mmol) was added dry Et_2O (20 mL), followed by Ac_2O (3.58 mmol) and DMAP (0.18 mmol). The reaction mixture was stirred at 25 °C for 2 h, and the solvent was evaporated in vacuo. To the resulting crude residue was added 1 N ethanolic $NaBH_4$ (4 mL) at 0 °C with stirring for 2 h (monitored by TLC). The mixture was acidified with 0.5 N HCl and extracted with Et_2O (3 × 20 mL), and the organic layers were washed with H_2O (1 × 20 mL). The crude was subjected to flash column chromatography, eluting with 10–30% EtOAc–hexane to give the nitroalkanes **29**–**35**.
(3*S*)-*N*-Benzyloxycarbonyl-3-amino-1-nitrobutane (29)
The β-hydroxy nitroalkane **22** (0.48 g, 1.79 mmol) was transformed according to the General Procedure C, which afforded the desired nitro alkane **29** as a clear oil (crystallized on standing; 0.31 g, 70%); mp 45–48 °C; $[\alpha]_D^{29}$ +9.2, (*c* 2.71, MeOH). HRMS (ESI^+): *m/z* calcd for $C_{12}H_{16}N_2O_4$ $[M + H]^+$: 253.1183; found: 253.1184. IR (NaCl): ν_{max} = 3392 (NH), 3349, 3336 (CH), 1680 (CO), 1550 (NO_2), 1242, 1064, 897 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.32 (5 H, s, ArH), 5.06 (2 H, s, $ArCH_2O$), 4.78 (1 H, d, *J* = 7.3 Hz, NH), 4.43–4.37 (2 H, m, CH_2NO_2), 3.82 (1 H, br s, NCH), 2.19–2.08 (2 H, m, $CH_2CH_2NO_2$), 1.20 (3 H, d, *J* = 6.6 Hz, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 155.9 (CO), 136.2, 136.2 (aryl C), 128.6, 128.2, 128.1 (aryl CH), 72.7 (CH_2NO_2) 66.9 ($ArCH_2O$), 45.1 (NCH), 34.4 ($CH_2CH_2NO_2$), 21.2 ($CHCH_3$).

(23) **General Procedure D – Preparation of the N-Protected β-Amino Acids 36–42**
To a solution of nitroalkane **29**–**35** (0.79 mmol) in DMSO (2 mL) was added $NaNO_2$ (2.37 mmol) and AcOH (7.9 mmol), and the reaction was heated to 40 °C for 20 h. After cooling to r.t., 1 N HCl was added to the yellow solution, stirring for

another 15 min, and the aqueous was extracted with Et_2O (3 × 15 mL). The organic layers were washed with H_2O (2 × 20 mL) and extracted with sat. $NaHCO_3$ solution (3 × 15 mL). The aqueous layers were acidified to pH 2 with 2 N HCl and then re-extracted with EtOAc (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was subjected to flash column chromatography, gradient eluting with 10–40% EtOAc–hexane to afford the N-protected β-amino acids **36**–**42**.

(3*S*)-*N*-Benzyloxycarbonyl-3-aminobutanoic Acid 36

Nitroalkane **29** (199 mg, 0.79 mmol) was transformed according to the General Procedure D, and afforded the desired β-amino acid **36** as a white solid (140 mg, 75%); $[\alpha]_D^{24}$ –12.5 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D^{27}$ –15.7 (*c* 1.0, $CHCl_3$).[17] ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.33–7.29 (5 H, m, ArH), 5.32 (1 H, NH), 5.08 (2 H, s, $ArCH_2O$), 4.10 (1 H, HNC*H*), 2.57 (2 H, s, CH_2), 1.26 (3 H, d, *J* = 6.7 Hz, CH_3).

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