An Approach to the Synthesis of *anti*-β^{2,3}-Amino Acids: Application of β-Trifluoroacetamidoorganozinc Reagents

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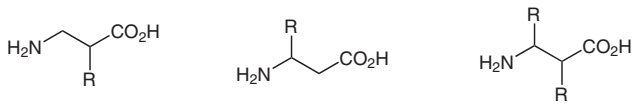
Abstract: An approach to the synthesis of *anti*-β^{2,3}-amino acids is reported. The key steps involve stereoselective lactone alkylation followed by ring opening with iodotrimethylsilane/ethanol to give iodo esters. Formation of the organozinc reagents from these iodo esters, followed by either Pd- or Cu-catalysed reaction with electrophiles gives protected β^{2,3}-amino acids. The *trans* stereochemistry in the enolate alkylation is confirmed for the allylated *anti*-lactone by X-ray crystallography.

Key words: amino acids, alkylations, cross-coupling, lactones, zinc

Although less abundant in nature than α-amino acids, β-amino acids are an important class of compound found in various biologically important molecules.[1–4] The synthesis of enantiomerically pure β-amino acids therefore continues to receive considerable interest. In addition to their presence in natural products, β-amino acids are also utilised as precursors to β-lactams. β-Amino acids found in free form exhibit interesting pharmacological properties and possess the ability to form stable secondary structures, which are more resistant to enzymatic degradation than their α-amino acid counterparts.[5–7] β-Amino acids can be classified according to the position of their substitution, as summarised by Seebach as β^2-, β^3- and β^{2,3}-amino acids (Figure 1).[1,2]



β^2-homo amino acid β^3-homo amino acid β^{2,3}-homo amino acid

Figure 1 β^2-, β^3-, and β^{2,3}-homo amino acids

Synthetic methods for the synthesis of β-amino acids have been extensively reviewed.[1–4,8] In the context of β^3-amino acid synthesis we have previously reported that alkyl iodides obtained from a selectively reduced *N*-Boc-protected L-aspartic acid derivative underwent Pd-catalysed cross-couplings with aryl iodides and acid chlorides to give β^3-substituted amino acid derivatives.[9,10] Interestingly, the corresponding *N*-TFA-protected alkyl iodide gave comparable yields to the Boc derivative.[11,12] Recently, we have applied this general approach to the synthesis of racemic β^2-amino acids.[13] We now report the extension of organozinc chemistry[14] to the synthesis of enantiomerically pure *anti*-β^{2,3}-amino acids.

We envisaged that the desired *anti*-β^{2,3}-amino acids **1** could be derived from the alkyl iodides **2** via formation of the corresponding organozinc reagent and subsequent reaction with a suitable electrophile (Scheme 1). The required iodide **2** may be obtained by iodotrimethylsilane-mediated ring opening of the lactone **3** and quenching of the resultant silyl ester with an alcohol.[15,16] Alkylation of the lactone **4** (itself derived from manipulation of L-aspartic acid) would give the precursor to the ring-opening reaction **3**. The appropriate choice of nitrogen protecting group is important since it must tolerate the conditions used for the iodotrimethylsilane ring opening in addition to being compatible with organozinc chemistry. It may also play a role in the facial selectivity of the reactions of the enolate derived from lactone **4**.[17,18]

Initially we explored the use of a carboxybenzyl (CBZ) protecting group, but this was not unsurprisingly incompatible with the key ring-opening step (**3** → **2**) using iodotrimethylsilane. A sulfonamide protecting group was then considered as it is known to tolerate these conditions.[15,16] Although we were able to synthesise the required alkyl iodide **2** (R = H, PG = Ts), reaction of this iodide with zinc resulted in recovery of large amounts of 4-methylphenylsulfonamide, arising from decomposition of the presumed organozinc reagent by β-elimination. Although we had previously shown that use of the strongly electron-withdrawing TFA group resulted in stabilisation of β-amino organozinc reagents (by suppressing internal coordination of the carbonyl group to zinc, and thereby changing the mechanism of the elimination),[12] use of the even more electron-withdrawing tosyl group presumably allows a faster elimination process. This observation is significant in defining the limits of introducing a more electron-withdrawing nitrogen protecting group to stabilise β-amino organozinc reagents. Ultimately, therefore, we turned to the TFA protecting group, in view of the fact that it promised to be compatible with enolate alkylation,[19] lactone ring opening using iodotrimethylsilane, and with organozinc reagent formation.[12]

Concurrent N-protection and cyclisation of L-aspartic acid to give cyclic anhydride **5** was achieved according to the literature procedure[20] by reaction with trifluoroacetic anhydride (TFAA, Scheme 2). Selective reduction of the

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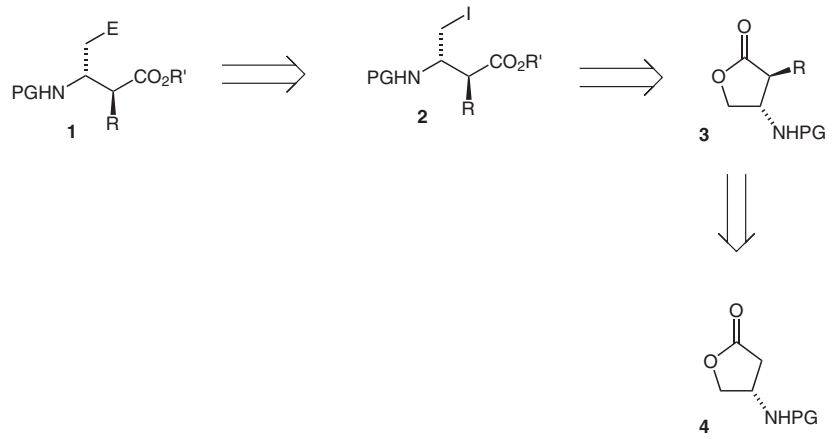
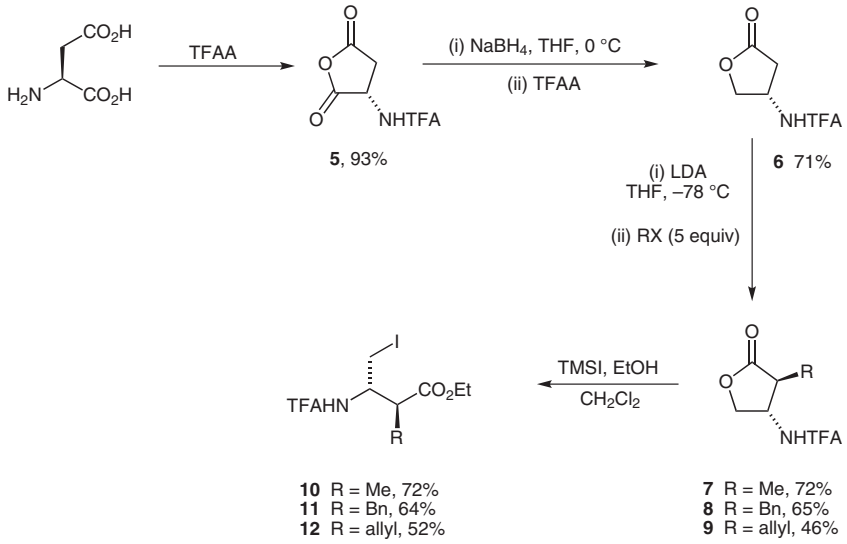


Scheme 1 Proposed route to protected *anti*-$\beta^{2,3}$-amino acids



Scheme 2 Synthesis of $\beta^{2,3}$-substituted alkyl iodides

carbonyl group adjacent to the N atom using $NaBH_4$ proceeded smoothly,[21] but required an additional recyclisation–N-protection step using TFAA to give lactone **6**. In addition, a small amount of compound resulting from reduction of the remote carbonyl group was isolated as a minor byproduct.

Alkylation of lactone **6** by treatment with LDA at –78 °C, followed by addition of an excess of methyl iodide, benzyl bromide, or allyl bromide at the same temperature, allowed introduction of the β^2 substituent (Me, Bn, allyl).[22] Under these conditions, a diastereoisomeric ratio of 11:1 (tentatively assigned as *trans*/*cis* by analogy with the literature) was observed for the methyl derivative **7**, and although crude ^{1}H NMR analysis of the allyl and benzyl derivatives **8** and **9** showed the presence of trace amounts of the minor *cis*-isomer, only the major *trans*-isomer was isolated. The yields quoted in each case are for the purified *trans*-isomer. A crystal structure of the allylated lactone **9** was obtained (Figure 2), confirming the *trans* relationship between the trifluoroacetamido group and the newly introduced allyl side chain.[23] It is interesting that successful benzylation of lactone **6** could be achieved in the absence of HMPA, which had been employed for benzylation of the corresponding Boc-[24] and CBZ-protected[25] lactones (**4**, PG = Boc or CBZ).

Pleasingly, ring opening of the methylated **7** and benzylated **8** lactones using iodotrimethylsilane and EtOH[15,16] was tolerated by the TFA protecting group and furnished the corresponding ethyl ester iodides **10** and **11** in fair yields.[26] Attempts to increase the modest yield obtained for the allyl derivative **12** resulted in unwanted side reactions involving the allyl group. However, under the conditions reported, the unreacted allylated lactone **9** could be recovered and recycled.

Conversion of the iodides **10** and **11** into the corresponding organozinc reagents proceeded smoothly using zinc activated with catalytic iodine in DMF.[27] Subsequent Pd-catalysed cross-coupling of each of the zinc reagents with aromatic iodides using $Pd_2(dba)_3$/P(*o*-tol)$_3$ gave the desired *anti*-$\beta^{2,3}$-amino acid derivatives in moderate to good yields over two steps from the starting alkyl iodides (Scheme 3, Table 1).[28] The mass balance arose from a

competing reaction pathway involving protonation of the organozinc reagents.

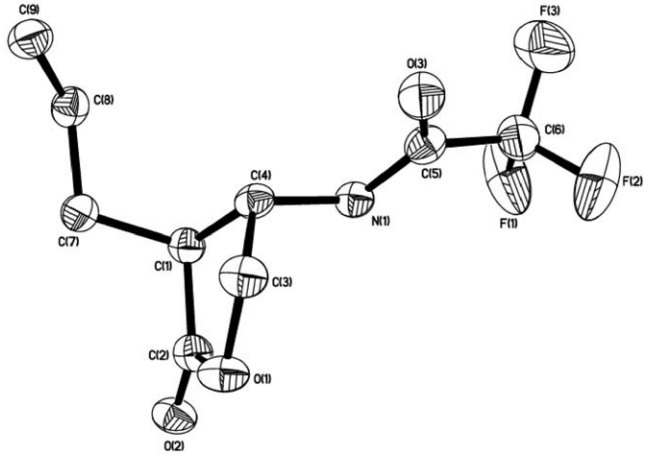
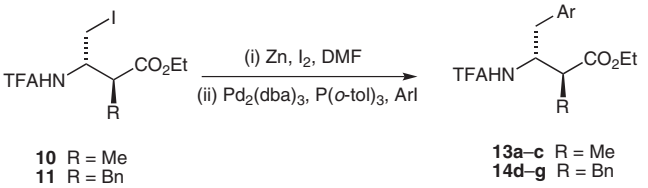


Figure 2 Crystal structure of allylated lactone **9**

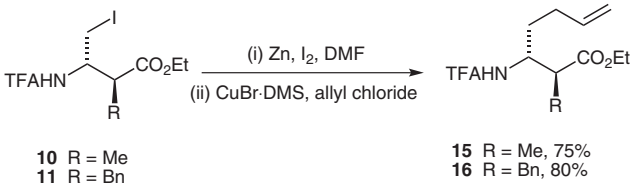


Scheme 3 Organozinc reagent formation from alkyl iodides **10** and **11** and subsequent Negishi cross-coupling

Table 1 Synthesis of Protected β^{2,3}-Amino Acids

Alkyliodide	Ar	Product	Yield (%)
10 (R = Me)	Ph	**13a**	71
10	3-$O_2NC_6H_4$	**13b**	51
10	4-FC_6H_4	**13c**	75
11 (R = Bn)	4-$O_2NC_6H_4$	**14d**	70
11	4-HOC_6H_4	**14e**	33
11	4-$MeOC_6H_4$	**14f**	63
11	4-BrC_6H_4	**14g**	55

Interestingly, the reaction of the organozinc reagent derived from the benzyl derivative **11** with 4-iodophenol gave a low yield of the desired product, in addition to isolation of a large amount of protonated organozoinc reagent. Although β^3-organozinc reagents have been shown to tolerate phenolic protons in Negishi reactions;[29] this result suggests that this particular organozinc reagent is more prone to protonation.[30,31] Cu-catalysed allylation reactions of the organozinc reagents derived from the iodides **10** and **11** gave the protected β^{2,3}-amino acids **15** and **16** in good yield (Scheme 4).[32]



Scheme 4 Organozinc reagent formation from alkyl iodides **10** and **11** and subsequent Cu-catalysed allylation

Attempted formation of the organozinc reagent derived from the allyl iodide derivative **12** over the usual time period led to recovery of large amounts of starting material in addition to only a small amount of the desired protonated compound **18**. Substantial amounts of a cyclic byproduct **17** were also observed. Extending organozinc reagent formation time to 18 hours led to complete conversion of the iodide **12**, but again only a small amount of the desired protonated product **18** was isolated. The cyclic byproduct **17** was now the major product, isolated as an approximately 2:1 mixture of diastereoisomers (Scheme 5). Related cyclisations are known.[33,34]

In conclusion, the TFA-protected, β^{2,3}-substituted iodides were prepared in four steps from L-aspartic acid. Formation of the organozinc reagent from the iodides **10** and **11** and subsequent Negishi reaction or Cu-catalysed allylation furnished the corresponding protected *anti*-β^{2,3}-amino acids in reasonable yield. The choice of protecting group was found to be crucial to the viability of this route, and indeed only the TFA group met the necessary requirements, tolerating both the iodotrimethylsilane ring-opening conditions and organozinc reagent formation. This result testifies to the usefulness of the TFA protecting group in the formation and reaction of β-amino organozinc iodides.[12]

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References and Notes

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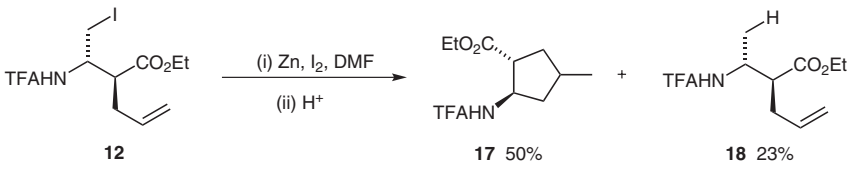

Scheme 5 Attempted formation of organozinc reagent from alkyl iodide **12**

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(22) **Procedure for Lactone Alkylation**
Using a minor modification of conditions already reported for the alkylation of dianions of γ-*N*-trifluoroacetyl amino acid esters,[19] *n*-BuLi (2.5 M in hexane, 5 mL, 12.5 mmol) was added dropwise to a stirred solution of DIPA (1.9 mL, 13.75 mmol) in THF (5 mL) at 0 °C. The resulting solution was stirred for 15 min before being cooled to –78 °C for the addition of the lactone **6** (985 mg, 5 mmol) in THF (28 mL). The reaction was stirred at the same temperature for a further hour before the electrophile (5 equiv) was added dropwise with careful monitoring of the internal temperature of the reaction to ensure it did not exceed –78 °C. After stirring at –78 °C for 18 h, the reaction was quenched with aq citric acid (10%, 30 mL) before being extracted with EtOAc (3 × 50 mL) and the organic fractions combined, washed with brine (2 × 30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.
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(26) **General Procedure for Iodotrimethylsilane Ring Opening**
Using conditions originally reported for the analogous *N*-tosyl-protected lactone,[15,16] iodotrimethylsilane (3 equiv) was added dropwise to a solution of the lactone (1 equiv) and EtOH (5 equiv) in dry CH_2Cl_2 under nitrogen at 0 °C. The reaction was stirred for 3 h at 0 °C and 16 h at r.t. until TLC analysis indicated complete consumption of starting material, at which point aq $Na_2S_2O_3$ solution (1 M) was added. The organic layer was separated and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography.
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(28) **General Procedure for Pd-Catalysed Cross-Coupling**
Zinc dust (195 mg, 3 mmol, 6 equiv) was placed in a dry 10 mL round-bottom flask with sidearm, containing a rugby-ball-shaped magnetic stirrer. The flask was flushed with nitrogen, and dry DMF (0.2 mL) was added under nitrogen via syringe followed by catalytic iodine (40 mg, 0.15 mmol, 0.3 equiv). Effervescence was observed and the DMF changed from colourless to yellow and back again. A solution of the appropriate alkyl iodide (0.5 mmol) in DMF (0.3 mL) under nitrogen was transferred to the activated zinc suspension via syringe. The solution was stirred at r.t., and the insertion proceeded with a noticeable exotherm. When the solution had cooled, $Pd_2(dba)_3$ (11.0 mg, 0.0125 mmol, 2.5 mol%), P(*o*-tol)$_3$ (15 mg, 0.05 mmol, 10 mol%) and the aryl iodide (1.3 equiv relative to the alkyl iodide) were added to the flask and the reaction stirred at r.t. overnight.
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(32) **General Procedure for Cu-Catalysed Allylation**
The organozinc reagent was formed as described above using zinc (6 equiv) and DMF (0.65 equiv) relative to the alkyl iodide. While the zinc insertion was in progress, CuBr·DMS (13 mol%) was dried gently under vacuum in a separate flask until it changed from a white to a light green powder. Dry DMF (0.65 equiv) was then added, followed by the allyl chloride (1.3 equiv). Once the zinc insertion reached completion, stirring of the reaction mixture was stopped to allow the zinc powder to settle, and the supernatant was transferred to the solution of allyl chloride and copper catalyst via syringe. After stirring for 18 h at r.t., EtOAc (10 mL) was added and the reaction stirred for a further 15 min. A further aliquot of EtOAc (30 mL) was added and the organic layer separated and washed successively with aq $Na_2S_2O_3$ solution (1 M, 2 × 30 mL), H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography.
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