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Easy access to orthogonally protected α-alkyl aspartic acid and α-alkyl asparagine derivatives by controlled opening of β-lactams

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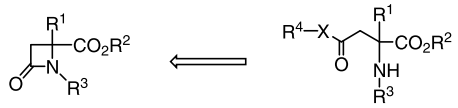
Abstract—The controlled opening of the N1–C2 bond in 1-carbamate-substituted 2-azetidinones derived from amino acids by *O*- and *N*-nucleophiles provided a straightforward access to orthogonally protected α-alkyl aspartic acid and asparagine derivatives. The use of DBU or sodium azide as additive is essential for expedient cleavage by amino acids to the corresponding β-aspartic acid dipeptides.

The discovery of $C^{\alpha,\alpha}$-disubstituted α-amino acids in natural bioactive compounds and their propensity to induce secondary structures when incorporated into peptides has resulted in an increased interest in novel methods for their synthesis.[1] In this respect, aspartic acid derivatives are especially interesting subjects for study because of their relevant role in physiological events and in the stabilization of reverse turns through interactions between backbone NH and side chain $C^{\gamma}O$ bonds.[2] Moreover, the Asp residue possesses multiple functional groups appropriate for structural diversification using parallel synthesis or combinatorial chemistry methodologies.[3] Several methods have been reported that describe the enantioselective synthesis of α-alkylated aspartic acid derivatives. These include alkylation of enolates derived from chiral imidazolidinones,[4] oxazolidinones,[5] oxazolones,[6] oxazinones,[7] and pyrazinones,[8] double alkylation of aldimine Schiff base of Gly esters under chiral phase-transfer catalysis,[9] and alkylation of Asn derivatives with 'self-regeneration' of the stereogenic center.[10] Other procedures comprise the asymmetric allylic alkylation with chiral palladium catalysts,[11] and the cycloaddition reaction to pyrazolines followed by alkaline fragmentation.[12] However, most of these methods required a final acid hydrolysis affording the corresponding α-alkyl aspartic acid derivative in fully deprotected form.

By other hand, β-lactams have long been recognized as useful synthetic intermediates for the preparation of a variety of compounds through selective bond cleavage of the 2-azetidinone ring.[13] In this sense, the opening of the N1–C2 bond by nucleophiles has been widely used for the preparation of β-amino acids and β-amino ketones.[14,15] The intramolecular version of this cleavage has served for the generation of different heterocyclic systems like bis-γ-lactams, indolizidines and pyrrolizidines.[16–18] In a similar way, the macrocyclization process based on the 2-azetidinone amide bond opening has been successfully used for the synthesis of several natural products and some internal β-turn mimetics.[19–21]

In connection with our current concern in conformationally constrained amino acids, we recently reported the first synthesis of 4-alkyl-4-carboxy-2-azetidinone derivatives **1** from commercially available amino acid alkyl esters.[22–24]



1 **2**: X = O, NH

These β-lactams have the appropriate substitution pattern to be considered as convenient precursors in the synthesis of α-alkyl Asp (X = O) and Asn (X = NH) derivatives **2**, by controlled aperture of the N1–C2 bond. Moreover, orthogonally protected Asp and Asn derivatives could be prepared by suitable selection of the R^2, R^3, and R^4 groups.

To explore this possibility, β-lactams **4** and **5**, derived from L-Phe-O^{t}Bu, were selected as model substrates, and then have been subjected to the action of different

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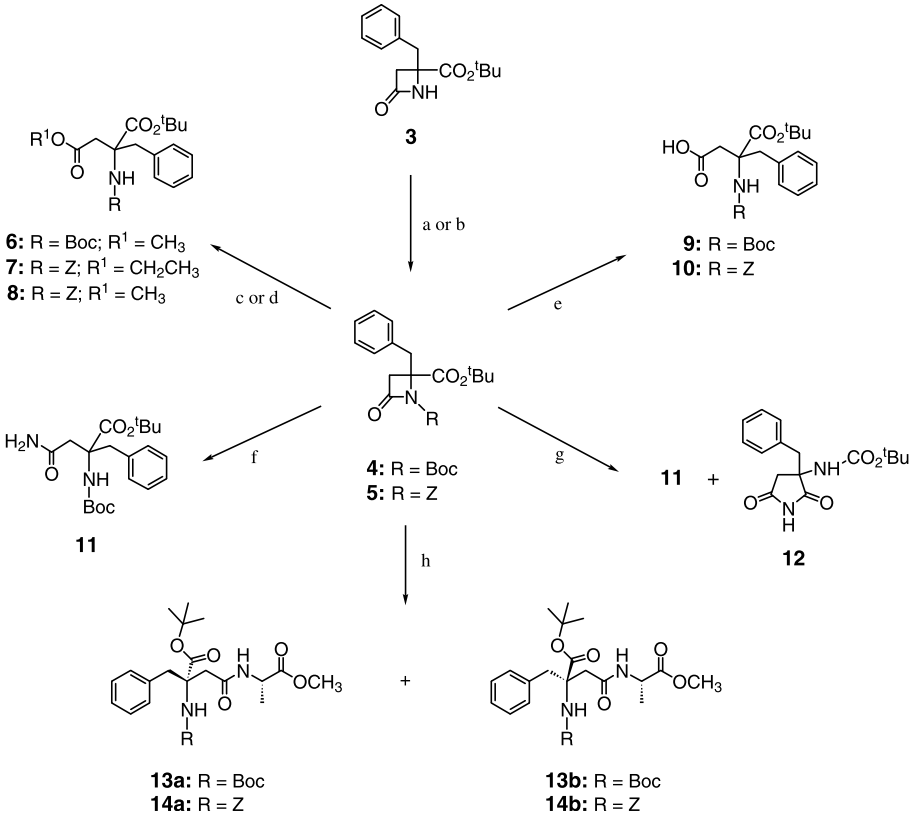
O- and *N*-nucleophiles. Compounds **4** and **5** were prepared in 75 and 76% yield by the treatment of the 2-azetidinone derivative **3** with *tert*-butyldicarbonate and benzyl chloroformate, respectively (Scheme 1). The *N*-urethane substituent in **4** and **5** (Boc and Z, respectively) has a double function, as an activating moiety facilitating the ring cleavage and, after the ring opening, as a protector of the resulting amino group.

Activated β-lactams **4** and **5** underwent regioselective alcoholysis, by treatment with alkoxides, to the expected fully protected α-benzyl Asp derivatives **6**



Scheme 1. *Reagents and conditions*: (a) $(^tBuO)_2CO/DMAP/CH_2Cl_2$; (b) $ZCl/DBU/CH_2Cl_2$; (c) R^1ONa/R^1OH; (d) $R^1OH/DBU/THF$; (e) 2N NaOH/THF; (f) satd $NH_3/MeOH$; (g) dilute $NH_3/MeOH$; (h) H-Ala-OMe/additive/solvent (see Table 1).

Table 1. Results of the controlled cleavage of *N*-carbamate-substituted 2-azetidinones by *O*- and *N*-nucleophiles

Entry	Starting compd	Cleavage conditions	Time	Final compd (yield %)[a]
1	**4**	MeONa/MeOH	24 h	**6** (75)
2	**5**	EtONa/EtOH	24 h	**7** (90)
3	**5**	MeONa/MeOH	24 h	**8** (89)
4	**5**	MeOH/DBU	10 min	**8** (96)
5	**4**	NaOH/THF	24 h	**9** (71)
6	**5**	NaOH/THF	24 h	**10** (92)
7	**4**	NH_3/MeOH (satd)	5 min	**11** (89)
8	**4**	NH_3/MeOH (dilute)	10 min	**11** (30)[b]
9	**4**	H-L-Ala-OMe/MeOH	6 days	**13ab** (53)[c]
10	**4**[d]	H-L-Ala-OMe/MeOH	6 days	**13ab** (49)[e]
11	**5**	H-L-Ala-OMe/DBU/THF	25 days	**14ab** (93)
12	**5**	H-L-Ala-OMe/DBU/THF	15 days[f]	**14ab** (85)
13	**5**	H-L-Ala-OMe/KCN/DMF	24 h[f]	**14ab** (40)[g]
14[b]	**5**	H-L-Ala-OMe/NaN_3/DMF	11 days	**14ab** (77)

[a] Yield of isolated compound.
[b] **12** (37%) was also obtained.
[c] Compound **6** (23%) was also isolated.
[d] 6 equiv. of the amino acid were used in this assay.
[e] Estimated by HPLC. Compound **6** (18%) was detected.
[f] Reaction at 60°C.
[g] The carboxylic acid **10** (40%) was also obtained.

(75%) and **7** (90%) (Scheme 1, Table 1). Alternatively, the alcoholysis could be performed in a faster and more productive way by reaction with the corresponding alcohol in the presence of DBU, as exemplified in the synthesis of compound **8** (Table 1, entries 3 and 4). The hydrolysis with NaOH afforded the corresponding diprotected Asp derivatives **9** and **10**, with a free carboxylate group at the side chain. All compounds resulting from the opening of the β-lactam ring showed in the ^{1}H NMR spectra the signal corresponding to the urethane NH proton.[25] In addition to that, a clear deshielding in the chemical sifts of the CO groups of the Asp derivatives with respect to these carbonyls in the starting β-lactams was observed in the ^{13}C NMR spectra.[25]

Encouraged by the good results of the reactions with *O*-nucleophiles, we then studied the 2-azetidinone ring opening by *N*-nucleophiles. Thus, the reaction of the β-lactam derivative **4** with satd ammonia in MeOH afforded Asn-derivative **11** in excellent yield (Table 1). This compound showed similar NMR characteristics to those previously indicated for the Asp derivatives resulting from opening with *O*-nucleophiles. It is interesting to note that dilute NH_3/MeOH solution gave a mixture of the expected compound **11** and the succinimide **12**. Considering that the formation of succinimides from Asn derivatives under basic conditions is sufficiently documented,[26] the generation of aspartimide **12** could be explained by cyclization of the acyclic derivative **11** in the reaction medium.

To explore the scope of the 1-carbamate substituted β-lactams as synthetic intermediates for the generation of molecular diversity, we next investigated the ring opening of compounds **4** and **5** with H-Ala-OMe, selected as model amino acid (Scheme 1, Table 1). The treatment of Boc-substituted derivative **4** with H-Ala-OMe in MeOH afforded a mixture of the expected diastereoisomeric β-aspartic dipeptides **13ab** and the Asp derivative **6**, resulting from the cleavage of the β-lactam ring by means of MeOH. From this result, it seems that the amino group of the amino acid is basic enough to catalyze the methanolysis reaction in competition with the amminolysis cleavage to the desired β-dipeptides. An increase in the amount of the amino acids to 6 equiv. did not improve the yield of compound **13** (entry 10). This reaction did not proceed by substitution of the MeOH with THF, probably as a result of the lower nuclephile character of the amino acid is this latter solvent. In good agreement with that, compound **14ab** was obtained in excellent yield when DBU was used as additive for the opening reaction of N-Z derivative **5** (Table 1, entry 11). Other additives such as KCN and NaN_3, successfully used for cleavage of β-lactam derivatives with both *O*- and *N*-nucleophiles,[27] gave to unlike results in our case. Thus, the reaction of compound **5** with H-Ala-OMe in the presence of KCN afforded the β-dipeptide derivative **14ab** in only 40% yield, along with an important amount of the aspartic acid derivative **10** (Table 1, entry 13). On the contrary, a similar reaction using sodium azide as additive resulted in compound **14ab** in 77% yield (entry 14). Since starting β-lactams **4** and **5** were 2:1 *S*/*R* mixtures of enantiomers, compounds **13** and **14** were obtained as diastereoisomeric mixtures in approximately the same ratio.

The feasibility of the Phe-derived β-lactams opening to produce orthogonally protected α-benzyl Asp and Asn derivatives could be extended to other α-alkyl analogues, just by using 2-azetidinones derived from other amino acids as starting materials. Moreover, taking into account that we have reported a general method for the asymmetric synthesis of our amino acid-derived β-lactams,[28] the procedures described here could have a widespread application to the generation of α-alkyl Asp/Asn derivatives in enantiomerically pure form.

Acknowledgements

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25. *Selected spectroscopic data of representative compounds*: **5**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47–7.02 (m, 10H, Ph), 5.34 (m, 2H, OCH_2), 3.53 (d, 1H, 3-H, $J=14.5$), 3.28 (d, 1H, 3-H, $J=14.5$), 2.93 (m, 2H, 4-CH_2), 1.42 (s, 9H, ^{t}Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.29 (COO), 162.11 (2-C), 148.46 (NCO), 134.91, 133.87, 130.32, 128.54, 128.45, 127.31 (Ar), 83.19 (C, ^{t}Bu), 68.08 (OCH_2), 61.21 (4-C), 44.48 (3-C), 35.85 (4-CH_2), 27.59 (CH_3, ^{t}Bu). **8**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–6.98 (m, 10H, C_6H_5), 5.90 (s, 1H, α-NH), 5.21 (d, 1H, CH_2 Z, $J=12.4$), 5.06 (d, 1H, CH_2 Z, $J=12.4$), 3.67 (d, 1H, β-H, $J=13.0$), 3.66 (d, 1H, α-CH_2, $J=16.5$), 3.62 (s, 3H, OCH_3), 2.99 (d, 1H, α-CH_2, $J=16.5$), 2.98 (d, 1H, β-H, $J=13.0$), 1.44 (s, 9H, ^{t}Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.49 and 170.04 (γ-CO and α-CO), 154.45 (NCO), 136.70, 135.11, 130.08, 128.44, 128.01, 127.02 (Ar), 83.40 (C, ^{t}Bu), 66.21 (CH_2 Z), 62.00 (α-C), 51.61 (OCH_3), 40.84 and 40.49 (β-C and α-CH_2), 27.80 (CH_3, ^{t}Bu). **10**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32–6.90 (m, 10H, C_6H_5), 5.83 (s, 1H, NH), 5.18 (d, 1H, CH_2 Z, $J=12.3$), 4.95 (d, 1H, CH_2 Z, $J=12.3$), 3.66 (d, 1H, α-CH_2, $J=16.5$), 3.56 (d, 1H, 2-H, $J=13.5$), 2.97 (d, 1H, α-CH_2, $J=16.5$), 2.90 (d, 1H, β-H, $J=13.5$), 1.24 (s, 9H, ^{t}Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.00 (γ-CO), 169.78 (α-CO), 154.48 (NCO), 135.60, 130.05, 128.44, 128.02, 127.06 (Ar), 83.58 (C, ^{t}Bu), 66.35 (CH_2 Z), 61.77 (α-C), 40.90 and 40.30 (β-C and α-CH_2), 27.71 (CH_3, ^{t}Bu).
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