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Unexpected formation of new chiral 3-amino-5-alkyl-2,5-dihydro-1*H*-pyrrolin-2-ones from *N*-Boc-α-amino esters

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Abstract—We describe a one-pot process involving the DiBAl-H reduction of the ester moiety of *N*-protected α-amino esters, followed by Horner–Wadsworth–Emmons olefination in the presence of the trimethyl ester phosphonoglycinate carbanion allowing the formation of new chiral 3-amino-5-alkyl-2,5-dihydro-1*H* pyrrolin-2-one **5**. The *Z*-enoate **4b**, which is formed during this reaction, could be converted into the corresponding lactam **5b** under UV irradiation with the presence of BuLi.

Recently, we have reported the synthesis of non-peptidic aminopeptidase A (APA) inhibitors,[1] which could constitute a new class of antihypertensive drugs acting on the central Renin–Angiotensin system.[2] In order to enhance their affinity for the targeted zinc metallopeptidase, APA, docking experiments of putative inhibitors were undertaken in leukotriene A4 hydrolase.[3,4] Indeed, this enzyme is also a monozinc aminopeptidase, which presents significant primary sequence homology with APA and was therefore used for the building of an APA model.[5] This docking study results in the identification of β-mercaptoacid **1** as a potential APA inhibitor acting as a bidentate with the catalytic zinc (Fig. 1). As part of our investigation into the synthesis of target molecule **1**, we imagined that the potential intermediate γ-amino-α,β-didehydroamino acid derivative **2** could be obtained from the corresponding *N*-benzylyoxycarbonyl-α-amino ester **3a** through DiBAl-H reduction of *N*-protected α-amino ester and trapping of the intermediate aluminate with the *N*-protected phosphonoglycinate trimethyl ester carbanion (Fig. 2).

This method is analogous to those developed by Takacs et al.[6] and David et al.[7] for the obtention of α,β-unsaturated esters, which allowed to avoid both racemization of the stereocentre and production of the α-amino alcohol. When the reaction was performed using **3a**, this one-pot process afforded a mixture consisting of the enoate **4a** and of the unexpected 3-amino-5-alkyl-2,5-dihydro-1*H*-pyrrolin-2-one **5a**, which was fully characterized by means of ^{1}H, ^{13}C NMR and MS. To the best of our knowledge, such highly functionalized pyrrolin-2-ones **5** were not previously described. Furthermore, these kind of five-membered ring lactams are found as substructures in numerous natural products bearing interesting pharmacological activities, among other examples are the potent cytotoxic and immunopressive lipopeptides microcolin A and B,[8] which contain a Pro-pyrrolin-2-one unit, although they do not contain an amino group in the 3-position of the ring. Moreover, such lactam derivatives bearing also an enamine functionality are useful building blocks in organic and asymmetric synthesis.[9] In this letter we report our initial discovery and the preliminary exploration of the scope of this one-pot process,[10] which was applied to various *N*-Boc-α-amino esters **3b–f** and to a fully protected dipeptide **3g** yielding new highly functionalized pyrrolin-2-one **5** as well as the obtention of compounds **4** (Fig. 2). We provide also a method for the conversion of the *Z*-enoates **4** into the lactam **5**.

The reduction in THF at −78 °C of *N*-Boc-α-amino esters **3** (1 equiv) with 2 equiv of DiBAl-H to the aluminoxyacetal was conducted in the presence of the phosphonoglycinate trimethyl ester carbanion (2 equiv) previously generated by addition of *n*-BuLi on

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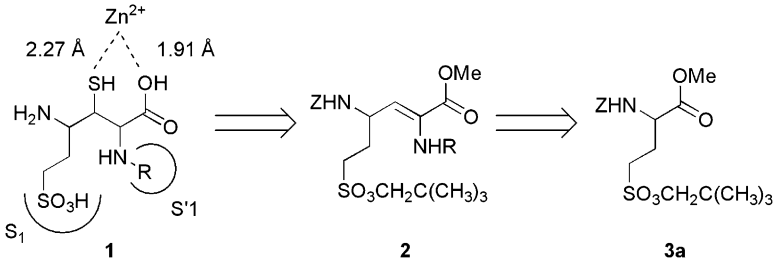

Figure 1. Putative APA inhibitor and its retrosynthetic scheme.

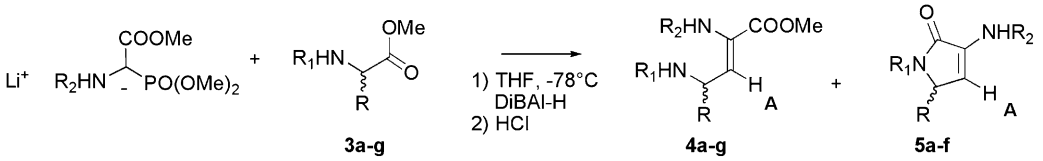

Figure 2. One-pot process for the synthesis of **4a**–**g** and **5a**–**f**. The various substituents R, R_1 and R_2 are defined in Table 1.

commercially available phosphonoglycine trimethylester. The intermediate aluminate then underwent a Horner–Wadsworth–Emmons (HWE) reaction. After 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature in order to complete the reaction thus affording a mixture of the *Z*-enoate **4** and the lactam **5** (Fig. 2 and Table 1). In all experiments, HPLC analysis performed on the reaction mixture have showed that the initially fully protected α-amino ester was totally consumed and that only the two expected products were formed in nearly equivalent proportions. In order to dispose of analytical pure material, the two products were purified and separated by semi-preparative HPLC yielding compounds **4** and **5** in 40% overall yield. Surprisingly, when the dipeptide **3g** was submitted to this one-pot process, only the orthogonally protected lactam **5g** was isolated.

Furthermore, it is noteworthy that the phosphonate anion reacted with the aluminate without epimerization of the stereocentre as shown by the reaction with the two enantiomers of *N*-Boc-phenylalanine methyl ester, which led to compounds **4b**–**c** and **5b**–**c**, respectively, showing, as expected, opposite optical rotation.

This reaction was further investigated starting from commercially available *N*-Boc-phenylalaninal **6**, in order to discard DiBAl-H in the cyclization (Table 2, Fig. 3). The *N*-Boc-phenylalaninal **6** was treated in the presence of 1 equiv of trimethylphosphonoglycinate trimethyl ester and solely the base amount was variable. If this reaction was performed in presence of DBU (1 or 2 equiv), only the *Z*-enoate **4b** was formed in almost quantitative yield independently of the number of equivalents of base (Table 2). The *Z* configuration was confirmed by NOE measurements. NOE's were observed between H_B and H_C but also between H_A and the hydrogens of the methyl ester moiety (Fig. 3). Furthermore the ethylenic proton chemical shift is analogous to those observed for previously described *Z*-didehydro-α-amino acid $\delta = 6.5$ ppm while for the *E* configuration the ethylenic proton is deshielded $\delta = 6.7$ ppm.[11] Contrary to the former trials, when the reaction was performed using *n*-butyl lithium (1 or 2 equiv) the two products **4b** and

Table 1. Yields, optical rotations and HPLC retention time for compounds **4a**–**f** and **5a**–**g**

Compound **4**	R	R_1	R_2	Configuration	$[\alpha]_D^{20}$	δ H_A[a]	Yield (%)	t_R[b]
a	$-CH_2CH_2SO_3CH_2C(CH_3)_3$	*Z*	Boc	*S*	—	6.12	17	10.1
b	$-CH_2Ph$	Boc	*Z*	*S*	+106 ± 1.2	6.16	25	9.3
c	$-CH_2Ph$	Boc	*Z*	*R*	−103 ± 0.9	6.16	22	9.3
d	–H	Boc	*Z*	—	—	6.47	11	5.1
e	$-CH_2-CH_2COO$*t*-Bu	Boc	*Z*	*S*	+100.9 ± 1.5	5.96	23	11.3
f	$-CH_2O$–*t*-Bu	Boc	*Z*	*S*	+94.5 ± 1.2	6.24	24	10.8
Compound **5**								
a	$-CH_2CH_2SO_3CH_2C(CH_3)_3$	*Z*	Boc	*S*	+6.5 ± 1	6.77	10	11.9
b	$-CH_2Ph$	Boc	*Z*	*S*	+21.7 ± 1.7	6.80	16	12.2
c	$-CH_2Ph$	Boc	*Z*	*R*	−20.6 ± 1.5	6.80	18	12.2
d	–H	Boc	*Z*	—	—	6.89	10	5.8
e	$-CH_2-CH_2COO$*t*-Bu	Boc	*Z*	*S*	+29.7 ± 1.0	6.81	14	12.8
f	$-CH_2O$–*t*-Bu	Boc	*Z*	*S*	+19.5 ± 0.2	7.01	10	11.9
g	$-CH_2Ph$	Boc-Ala	*Z*	*S*–*S*	+61.6 ± 0.6	6.95	14	12.2

[a] Chemical shift (ppm) recorded in $CDCl_3$.
[b] HPLC retention time (t_R, min) Kromasil C18 5μ 100 Å with a mobile phase consisting of 30% H_2O, 70% CH_3CN.

Table 2. Effect of the base on the formation of compound **4b** and **5b**

Assay	Base	Equiv	Reaction times and temperature	t_R and %,[a] **yield of 4b**	t_R and %,[a] **yield of 5b**
1	DBU	1	1 h 25 °C	9.3 (100%)	Not detected
			+2 h 25 °C	9.3 (100%), **93**	Not detected
2	DBU	2	1 h 25 °C	9.3 (100%)	Not detected
			+2 h 25 °C	9.3 (100%), **97**	Not detected
3	BuLi	1	1 h −78 °C	9.3 (70%)	12.3 (30%)
			+2 h 25 °C	9.3 (68%), **38**	12.3 (32%), **17**
4	BuLi	2	1 h −78 °C	9.3 (66%)	12.3 (34%)
			+2 h 25 °C	9.3 (75%), **40**	12.3 (25%), **16**

[a] t_R: HPLC retention time (min) Kromasil C18 5μ 100 Å with a mobile phase consisting of 30% H_2O, 70% CH_3CN; %: area of the eluted peaks.

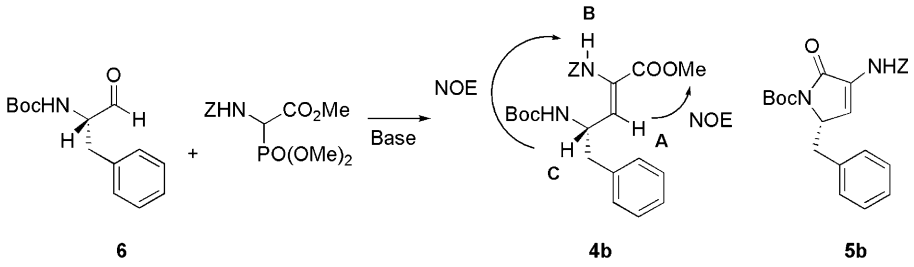

Figure 3. Synthesis of **4b** and **5b** starting from *N*-Boc-phenylalaninal **6**.

5b were isolated and the overall yield 55% was slightly improved (Table 2). This result are consistent with previous reports where DBU under salt free conditions had afforded *Z*-selective reactions[12] while alkyl lithium reagents afforded the geometrical mixture of (*Z*) and (*E*)-enoates in 1.5 *Z*/*E* ratio.[11–13] Furthermore, it is known that HWE reactions lead to the formation of the thermodynamically more favoured alkene,[14–16] which in our case corresponds to compound **4a** and that the products of this reaction do not undergo *E*/*Z* isomerization[17] under the reaction conditions.

Therefore, taking into account this last fact, but also that compounds **4b**/**5b** are obtained in a ratio comparable to those observed when alkyl lithium are used in classical HWE reaction and finally the *E* configuration of the enamine bond in compound **5b**, we postulated that the (*E*)-enoate **7** (Fig. 4) was the reaction intermediate, which cyclized in the presence of a base to yield lactam **5b**. Since in the reaction with 1 equiv, there is no BuLi left after the deprotonation of the phosphoglycinate, therefore methylate is probably responsible for the postulated deprotonation–cyclization sequence (Table 2). In order to confirm this hypothesis and to find a way to convert the *Z*-enoate **4b** into the more original lactam **5b**, compound **4b** was submitted to a photoisomerization under UV irradiation in THF at −78 °C in the presence of *n*-BuLi (Fig. 4). After 6 h of reaction and usual workup, analysis of the crude reaction mixture by LC–MS allowed the detection of two products. The first eluted peak with an area of 75% (50% yield after semi preparative HPLC) corresponded to the initial (*Z*)-enoate **4b** (MS: 477 $M+Na^+$) and the second eluted peak to the cyclized lactam **5b** (area: 25%, 20% yield after semi preparative HPLC, MS: 445 $M+Na^+$). This could be interpreted as the result of the photoisomerization of the *Z*-enoate **4b** to the *E*-enoate, which spontaneously cyclized to the lactam **5b** (Fig. 4). Furthermore when the *Z*-enoate **4b** was allowed to react with *n*-BuLi in the absence of UV irradiation, product **4b** was recovered unchanged after 6 h. Therefore, this method could constitute an alternative to obtain the pyrrolone **5** starting from the *Z*-enoate **4**.

In the course of this work, we have shown that new chiral 3-amino-5-alkyl-2,5-dihydro-1*H*-pyrrolin-2-ones **5** are easily obtained in a one-pot process starting from commercially available products. Despite the relatively

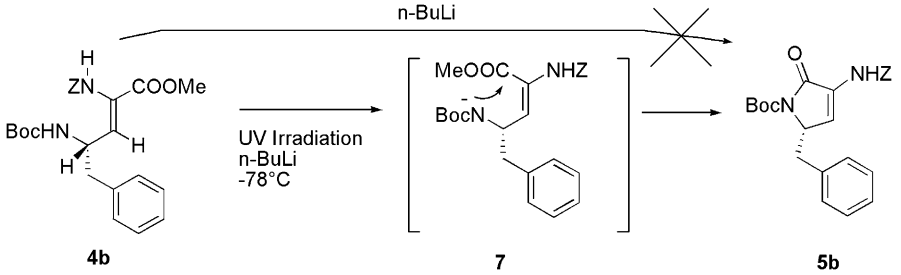

Figure 4. Photoisomerization of the *Z*-enoate **4b** and conversion in **5b**.

low yields resulting from tricky HPLC purifications due to the overlapping peaks of compounds **4** and **5**, this reaction has a relatively broad application, since, we have successively applied this process not only to *Z*- or Boc *N*-protected α-amino esters bearing various lateral functionalized or non functionalized side chains, but also to a dipeptide.

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10. General procedure for the obtention of **4** and **5**: A solution of *n*-butyl lithium 1.6 M in hexane (0.62 mL, 1 mmol, 2 equiv) is added at −78 °C to a solution of *N*-benzyloxycarbonyl-phosphonoglycine trimethyl ester (0.331 g, 1 mmol) in 3 mL anhydrous THF. After 30 min stirring, compound **3** (0.5 mmol) in 1 mL anhydrous THF was added, followed immediately by a dropwise addition of 0.66 mL, 1 mmol of DiBAl-H solution (1.5 M in toluene). The resulting mixture was stirred for 4 h at −78 °C and at room temperature for 1 h. The solvents were removed under reduced pressure. Diethylether (10 mL) and 5 mL of 1 M hydrochloric acid were added to the residue and the mixture was stirred for 1 h. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. After column chromatography on silica gel (*c*-hexane/ethyl acetate 8:2) the products are isolated as an oil. Analytical pure material were obtained by semipreparative HPLC Kromasil C18 5μ 100 Å, CH_3CN 80%.
Compound **4b**: $R_f = 0.06$ (*c*-hexane/ethyl acetate = 8:2); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 9H, NCOOC(CH_3)$_3$), 2.85 (dd, 1H, $J = 13.9$ Hz, $J = 7.8$ Hz, CH_2Ph), 2.98 (dd, 1H, $J = 12$ Hz, $J = 5.7$ Hz, CH_2Ph), 3.73 (s, 3H, OCH_3), 4.63 (td, 1H, NC*H*), 4.68 (d, 1H, $J = 7.5$ Hz, BocN*H*), 5.15 (s, 2H, OCH_2Phe), 6.17 (d, 1H, $J = 8.7$ Hz, C*H*=C), 7.17–7.36 (m, 10H, *H* arom), 7.59 (s, 1H, N*HZ*); ^{13}C NMR ($CDCL_3$, 100 MHz): δ 28.4 (CH_2COOC(CH_3)$_3$), 38.8 (CH_2Ph), 48.9 (N*C*H), 52.5 (COOCH_3), 67.4 (OCH_2Phe), 80.5 ((CH_3)$_3$*C*OCON), 121.6 (*C*H=C), 127.2 (*C* arom), 128.4 (*C* arom), 128.7 (*C* arom), 128.8 (*C* arom), 128.9 (*C* arom), 129.5 (*C* arom), 129.7 (*C*=CH), 135.7 (*C* arom), 149.2 (*t*-BuO*C*ON), 153.2 (*C*OOCH_2Phe), 165.2 (*C*OC=CH); HRMS (ESI): 477.1980 calcd for $C_{25}H_{30}N_2O_6Na^+$: 477.2002; $[\alpha]_D^{20}$ +106±1.2 (*c* 0.2 in $CHCl_3$).
Compound **5b**: $R_f = 0.13$ (*c*-hexane/ethyl acetate = 8:2); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.63 (s, 9H, NCOOC(CH_3)$_3$), 2.76 (t, 1H, $J = 12$ Hz, CH_2Ph), 3.52(d, 1H, $J = 12$ Hz, CH_2Ph), 4.71 (d, 1H, $J = 5.7$ Hz, NC*H*), 5.17 (s, 2H, OCH_2Phe), 6.80 (s, 1H, C*H*=C), 7.0–7.36 (m, 11H, *H* arom, N*HZ*); ^{13}C NMR ($CDCL_3$, 100 MHz): δ 28.4 (CH_2COOC(CH_3)$_3$), 39.1 (CH_2Ph), 60.7 (N*C*H), 67.7 (OCH_2Phe), 84.0 ((CH_3)$_3$*C*OCON), 121.6 (*C*H=C), 127.2 (*C* arom), 128.4 (*C* arom), 128.7 (*C* arom), 128.8 (*C* arom), 128.9 (*C* arom), 129.5 (*C* arom), 129.7 (*C*=CH), 135.7 (*C* arom), 149.2 (*t*-BuO*C*ON), 153.2 (*C*OOCH_2Phe), 165.2 (*C*OC=CH); HRMS (ESI): 445.1722 calcd for $C_{24}H_{26}N_2O_5Na^+$: 445.1739; $[\alpha]_D^{20}$ +21.7±1.7 (*c* 0.2 in $CHCl_3$).
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