2-Phenyl-tetrahydropyrimidine-4(1H)-ones – cyclic benzaldehyde aminals as precursors for functionalised β²-amino acids

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Abstract

Novel procedures have been developed to condense benzaldehyde effectively with β-amino acid amides to cyclic benzyl aminals. Double carbamate protection of the heterocycle resulted in fully protected chiral β-alanine derivatives. These serve as universal precursors for the asymmetric synthesis of functionalised β²-amino acids containing acid-labile protected side chains. Diastereoselective alkylation of the tetrahydropyrimidinone is followed by a chemoselective two step degradation of the heterocycle to release the free β²-amino acid. In the course of this study, an L-asparagine derivative was condensed with benzaldehyde and subsequently converted to orthogonally protected (R)-β²-homoaspartate.

Introduction

Monosubstituted β-amino carboxylic acids can be classified according to their substitution pattern into α-substituted “β²-amino acids” and β-substituted “β³-amino acids” [1]. Oligomers of these β-amino acids are called “β-peptides” and tend to form distinct and stable secondary structures even at a very short chain lengths [2,3]. β-Peptides are metabolically stable peptidomimetics that have proved to be inert to enzymatic proteolysis both in vitro [4,5] and in vivo [6]. As a first biologically active example, the β-tetrapeptide Ac-β³-hThr-β³-hLys-β³-hTrp-β³-hPhe-NH₂ was found to bind to a human somatostatin receptor with nanomolar affinity [7-9]. Despite their interesting properties, β²-amino acids in particular occur only rarely in nature. Several peptidic natural products contain 3-amino-2-methylpropionic acid (β²-homoalanine) as a building block [10]. Examples are
cryptophycin-1 (a highly cytotoxic depsipeptide produced by cyanobacteria Nostoc sp. GSV224 and ATCC53789) [11-14] as well as a class of lipopeptides isolated from various fungi, comprising topostatin (a topoisomerase I and II inhibitor) [15], YM-170320 (an inhibitor of ergosterol biosynthesis) [16], and fusaristatins A and B [17].

β²-Homoamino acids can be synthesised by Arndt–Eistert homologation of the corresponding proteinogenic α-amino acids [18-20]. Contrary to that, no procedure is known yet to enantioselectively convert α-amino acids into their β²-homologues – although this goal has been achieved diastereoselectively under auxiliary control [21,22]. A vast number of synthetic approaches to β²-(homo)amino acids have been developed so far, but the majority of these procedures are limited to α-alkyl substituted β²-amino acids – mostly due to harsh conditions of auxiliary cleavage or limited substrate tolerance [10,23,24]. Diastereoselective total synthesis starting from N-acylated Evans’ type auxiliaries turned out to be the only universal route to β²-analogues of the 20 most common proteinogenic α-amino acids. (For a recent overview on β²-amino acid syntheses see ref. [23].)

The tetrahydropyrimidine-4(1H)-one 2 developed by Juaristi et al. [25,26] and Konopelski et al. [27,28] represents a chiral cyclic β-alanine derivative that serves as a straightforward β²-amino acid precursor (Scheme 1A). Following the principle of self regeneration of stereogenic centres (SRS) proposed by Seebach [29], condensation of L-asparagine and pivalaldehyde yields N,N'-acetal 1, which is converted to 2 by subsequent oxidative decarboxylation [25,28,30-33], hydrogenation of the resulting olefinic double bond [25-27,31,34,35], and final N,N'-protection. Compound 2 proved to be a versatile β²- and β²,²- amino acid precursor. Monoalkylation of 2 takes place in high yields and with high trans-selectivity. Inversion of the introduced stereogenic centre via diastereoselective protonation [34] as well as α,α-dialkylation [36] both proceed smoothly. However, complete hydrolysis of the alkylated N,N-acetal requires refluxing in concentrated aqueous mineral acid. Therefore, precursor 2 can only be applied for the synthesis of target compounds without acid labile functional groups. Seebach et al. partly circumvented this problem by cleaving α-alkylated imino esters of tetrahydropyrimidine-4-ones to corresponding β²-amino acid methyl esters under markedly milder acidic conditions [37].

Nevertheless, a derivative of 2 being cleavable under neutral or slightly basic conditions was still unknown. Such a precursor would allow the synthesis of β²-amino acids containing e.g. tert-butyl protected side chain functions. Amino acids protected like that are particularly suitable for solid phase peptide synthesis and are thus highly desirable. Our novel ring cleavage concept includes the protection of both ring-nitrogen atoms as carbamates (Scheme 1C). Similar to the cleavage conditions of Evans’ auxiliaries (Scheme 1B) [38], the tetrahydropyrimidinone ring could now be regioselectively opened by treatment with lithium hydroperoxide. If the original C²-tert-butyl function was additionally substituted by a phenyl group through replacement of pivalaldehyde by benzaldehyde, this structural modification would facilitate a final release of the β²-amino acid by hydrogenolysis of all remaining benzyl-type N-protective groups.

**Scheme 1:** Selectively cleavable β²-amino acid precursors: Structures and reactivities of 2-tert-butyl-tetrahydropyrimidine-4(1H)-ones (A), N-acylated Evans auxiliaries (B), and novel Cbz-protected 2-phenyl-tetrahydropyrimidine-4(1H)-ones (C).

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**A:** Juaristi et al.

![Diagram A](image1)

**B:** Evans et al.

![Diagram B](image2)

**C:** combination of concepts A and B

![Diagram C](image3)
Results and Discussion

Cyclocondensation of benzaldehyde and β-amino acid amides to 2-phenyl-tetrahydroprymidine-4-(1H)-ones is problematic, since acyclic resonance stabilised Schiff bases are preferentially formed. Consequently, one pot cyclisation protocols employing conditions such as KOH in protic solvents deliver the desired six-membered ring only in unsatisfactory yields [30, 39]. An alternative approach to cyclise benzaldehyde-derived imines consists of a 4-DMAP catalysed N-acylation reaction with acyl chlorides and usually affords the target compounds in moderate yields [39,40].

We chose Nα-Cbz-protected β-alanine amide (3) as starting material for the synthesis of the 2-phenyltetrahydroprymidine-4(1H)-one rac-4 to circumvent the difficulty of cyclising stabilised benzyl imines. Cyclocondensation was successfully carried out under two different reaction conditions (Scheme 2). On the one hand, 3 was reacted with benzaldehyde or with the corresponding dimethylacetal in refluxing toluene in the presence of a catalytic amount of p-TsOH. The water or methanol formed during condensation was distilled azotropically from the reaction mixture. An even more effective method turned out to be the BF₃·Et₂O-mediated condensation of 3 with benzaldehyde or benzaldehyde dimethylacetal. Since the Lewis acid serves both as activating agent and as irreversible water/methanol trapping agent, two equivalents of it are necessary to drive the reaction to completion. The 2-phenyl-tetrahydroprymidine-4-one rac-4 obtained by either of the two methods can be purified by crystallisation or chromatography. Compound 4 proved to be stable to air moisture at room temperature. Despite the success in condensing 3 and benzaldehyde (dimethylacetal), all attempts to condense 3 with closely related acetoephene dimethylketal did not lead to any cyclisation product.

Scheme 2: Cyclocondensation of Cbz-PAla-NH₂ (3) and benzaldehyde. a) [p-TsOH], toluene, reflux, Dean–Stark trap, 3 h; b) BF₃·Et₂O (2.0 equiv), CH₂Cl₂, rt, 16 h.

To facilitate our selective ring opening concept, the N³-nitrogen of 4 had to be protected as a carbamate. While the introduction of a Boc-protecting group was straightforwardly carried out under mild conditions by reaction of 4 with Boc₂O/DMAP in acetonitrile [41], comparative Cbz-protection required more drastic conditions, i.e. deprotonation of 4 with n-BuLi and subsequent reaction with Cbz-Cl (Scheme 3).

Finally, enantiopure 2-phenyltetrahydroprymidine-4(1H)-ones were successfully synthesised via a chiral pool approach by condensing Cbz-L-Asn-OAll (8) with benzaldehyde dimethylacetal (Scheme 4). Compared to the respective cyclisation reaction starting from 3, complete conversion of 8 required a larger excess of BF₃·Et₂O, most probably due to the larger number of Lewis basic functions present in the starting material. Starting at −30 °C, the temperature of the reaction mixture had to be raised to −15 °C to enhance the solubility of the starting material as well as to increase the otherwise very low reaction rate. Cyclocondensation afforded the trans-configured major product (2R,6S)-9 and the cis-configured minor diastereomer (2S,6S)-9 in a ratio of 64 : 36 (28% de). Both compounds were obtained as colourless thick oils after separation by column chromatography. Since the cyclisation reaction was carried out under kinetic control, its moderate trans-selectivity contrasts to the high cis-selectivity observed for the thermodynamically controlled cyclocondensation of potassium asparagine and aliphatic aldehydes [25,27,28,31,34,35].
Scheme 4: Synthesis of enantiopure 2-phenyl-tetrahydropyrimidine-4(1H)-ones. a) PhCH(OMe)₂, BF₃·Et₂O (6.0 equiv), CH₂Cl₂, −30 °C → −15 °C, 16 h; b) 1. [Pd(PPh₃)₄]₂, morpholine, THF, rt, 1 h; 2. DIB, I₂, CH₂Cl₂, rt, 4 h, then BF₃·Et₂O, rt, 1 h; c) Ni(OAc)₂·4H₂O/NaBH₄, MeOH/THF, 0 °C, 10 min; d) Boc₂O, DMAP, CH₃CN, 16 h, rt.

En route to the target compound (R)-4, the allyl ester (2R,6S)-9 was cleaved in a Pd(0)-catalysed reaction [43]. In accordance with a literature procedure, the intermediate carboxylic acid was directly subjected to an oxidative decarboxylation [30]. The iodoalkene 10 was obtained by reaction of the free carboxylic acid with diacetoxyiodosobenzene (DIB) in the presence of iodine and BF₃·Et₂O. The absolute configuration of the highly crystalline compound 10 was determined in the course of an X-ray analysis [44]. The six-membered heterocycle of 10 shows a flattened boat- to envelope-like conformation. Five of the six ring atoms are almost coplanar while the C₂-atom and the pseudoaxial C₂-phenyl group are situated above the plane (Figure 1).

Figure 1: X-ray crystal structure of 10 [44].

In order to convert the iodinated dihydropyrimidinone 10 into the fully saturated tetrahydropyrimidinone (R)-4, selective hydrodehalogenation and reduction of the double bond had to be accomplished. Chemoselective reduction of 10 was carried out by reaction with sodium borohydride in the presence of Ni(OAc)₂. The “nickel boride” formed as black precipitate serves as a highly active hydrogenation catalyst, whereas an excess of NaBH₄ serves as hydrogen source [45,46]. The reaction reaches completion within ten minutes at 0 °C – virtually without formation of by-products. A similar procedure has formerly been employed by Bella et al. for the reduction of α-halogenated, α,β-unsaturated lactones [47].

The racemic fully protected heterocycle rac-5 as well as the enantiopure compound (S)-5 derived from (R)-4 were both used as starting materials for diastereoselective alkylation experiments. Attempts to enolise 5 at −78 °C by reaction with NaHMDS or LiHMDS, followed by addition of benzyl bromide did not lead to any alkylation product. Instead, the starting material was re-isolated. Addition of sodium iodide to the reaction mixture for an in situ conversion of the alkyl bromide to the alkyl iodide [48] did not increase reactivity. The alkylation reaction started to proceed only after warming the lithium enolate solution to −55 °C, but still remained incomplete after 20 h reaction time. By adding DMPU as co-solvent [49], the alkylation was typically complete within 16 h at −55 °C. The alkylation products 11a-d were obtained in good yields and with high diastereomeric excesses around 90% (see Scheme 5). However, none of the diastereomeric mixtures was separable by column chromatography on silica gel. Although in general no α,α-dialkylation products were detected by ESI-mass spectrometry, HPLC-analysis of 11d revealed the existence of a less polar by-product (see Supporting Information File 1), which
Figure 2: Comparison of coupling constants (C₅-C₆-ABX system) within the ¹H-NMR spectra of literature known compounds trans-12 and cis-12 (A) [36] to those of alkylation products 11a-d and 13 (B).

Table 1: Coupling constants (Hz) for compounds 11a-d and 13. The values are given for ¹H-NMR spectra in CDCl₃ solution.

| Compound | ³JAX (Hz) | ³JBX (Hz) |
|----------|-----------|-----------|
| 11a      | 10.5      | 7.8       |
| 11b      | 10.9      | n. d.     |
| 11c      | 10.2      | 8.0       |
| 11d      | 11.5      | 8.0       |
| 13       | 10.5      | 7.8       |
| 11b      | 10.9      | n. d.     |
| 11c      | 10.2      | 8.0       |
| 11d      | 11.5      | 8.0       |

Notes: a) TFA, CH₂Cl₂, 0 °C, 1 h, n. d. = not detectable

Overall, chemical shifts and coupling constants are quite similar for both types of compounds, indicating an analogous ring conformation in CDCl₃ solution. In case of 11d, ³J-coupling constants within the ABX-system of the three protons at C₅ and C₆ parallel those of the syn-configured compound cis-12, but not those of the anti-configured compound trans-12 [36]. The high value of the ³JAX-coupling constant of around 10 Hz does not significantly change after removing the N³-Boc-protective group, as exemplified by compounds 11b/13.

Interestingly, alkylation of 5 turned out to be syn-selective, whereas literature known alkylations of the closely related compound 2 selectively afford anti-configured alkylation products [25,26,35]. First hints at the stereochemical outcome of the alkylation reaction were deduced by comparing ¹H NMR spectra of compounds 11a-d with those of literature known N³-methylated alkylation products 12 and 14 (Figure 2) [36]. Overall, chemical shifts and coupling constants are quite similar for both types of compounds, indicating an analogous ring conformation in CDCl₃ solution. In case of 11d, ³J-coupling constants within the ABX-system of the three protons at C₅ and C₆ parallel those of the syn-configured compound cis-12, but not those of the anti-configured compound trans-12 [36]. The high value of the ³JAX-coupling constant of around 10 Hz does not significantly change after removing the N³-Boc-protective group, as exemplified by compounds 11b/13.

The decisive influence of N-acyl substituents within cyclic five- and six-membered N,N- and N,O-acetals on the stereochemical course of alkylations and ring closure reactions is a long known and frequently observed phenomenon (for an overview, see ref. [50]). The at first sight surprising differences in stereochemical outcome of alkylations of 2 and 5 could be explained by comparing their proposed enolate conformations (see Figure 3). In case of 2-Li, the pseudo-axial C₂-tert-butyl function effectively shields one diastereotopic face, thereby enforcing an electrophilic attack at the opposite side of the ring [26]. In contrast to that, the sterically less demanding C₂-phenyl group within 5-Li does not completely shield its diastereotopic half room. Instead, the opposite face is more efficiently shielded by the two bulky N¹- and N³-urethanes. This hypothesis is supported by the fact that alkylation of the N³-Cbz-protected heterocycle rac-6 resulted in a decreased diastereoselectivity compared to reactions of the N³-Cbz-protected compound 5 (results not shown here). The steric hindrance caused by the C²-phenyl ring may nevertheless account for the decrease in reactivity and diastereoselectivity being observed for alkylation of 5 compared to alkylations of 2.

To release the tert-butyl protected β²-homoaspartate, its precursor 11d was regioselectively degraded in a two step procedure (Scheme 6). Treatment of 11d with LiOH/H₂O in THF/H₂O afforded the ring opening product 15. Although 15 can be purified by column chromatography, it turned out to be only moderately stable and slowly degraded to Cbz-(R)-β²hAsp(Or-Bu)-OH, benzaldehyde and tert-butyl carbamate upon prolonged exposure to air moisture. Therefore, unpurified 15 was directly converted to the free amino acid by means of hydrogenation. Subsequent Fmoc-protection afforded the orthogonally protected target compound Fmoc-(R)-β²hAsp(Or-Bu)-OH (16). The specific rotation of the (R)-configured compound 16 in CHCl₃ showed a value of −1.2, whereas Seebach et al. report a value of +1.4 for the corresponding (S)-enantiomer [51]. Thus, the determined optical activity of 16 corresponds well to its expected enantiomeric excess of 89% and doubtlessly confirms the anticipated stereochemistry of the alkylation reaction.
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Supporting Information
Supporting Information File 1
Detailed synthetic procedures and characterisation data for all new compounds reported in this paper.

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