Tetrahedron 68 (2012) 9578–9582

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective multigram-scale synthesis of *cis*- and *trans*-β-phenylproline derivatives

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ARTICLE INFO

Article history:
Received 10 August 2012
Accepted 12 September 2012
Available online 19 September 2012

Keywords:
Non-proteinogenic amino acid
Proline analogue
β-Substituted proline
3-Phenylproline
Stereoselective synthesis
Vinyl triflate

ABSTRACT

Efficient routes for the gram-scale preparation of the proline analogues that bear a phenyl substituent attached to the pyrrolidine β carbon (*cis*- and *trans*-β-phenylproline) have been developed. The *cis* derivative was synthesized from *N*-Boc-β-alanine in six steps and 78% overall yield. The generation of a vinyl triflate with full regiochemical control together with a high-yielding cross-coupling reaction and a completely stereoselective hydrogenation are at the basis of the high efficiency of the procedure. Epimerization of the *cis* β-phenylproline derivative with lithium bis(trimethylsilyl)amide provided access to the *trans* isomer.

1. Introduction

The wide range of chemical, pharmacological and biotechnological applications of proline[1] has motivated the development of synthetic methodologies for the preparation of a vast range of proline analogues.[2] In particular, very significant advances have been made in the synthesis of proline analogues with modified conformational and functional properties for the development of peptide-derived therapeutics.[3] The reason for this is the key role of proline in defining the secondary structure, and hence the biological behaviour, of peptides.[4]

In this context, proline analogues that bear side chains belonging to other proteinogenic amino acids have elicited particular interest.[3d] These proline-based residues, when incorporated into peptides as surrogates of the coded amino acids, not only place constraints on the peptide backbone but also serve as probes to investigate the effect caused by the functional group and the conformation. Such combination of structural and functional properties makes substituted prolines very helpful tools for elucidating receptor-bound bioactive conformations. Moreover, some prolines functionalized with groups present in the side chains of other proteinogenic amino acids are naturally occurring compounds or constitute a part of bioactive natural products.[5]

Among substituted prolines, β-phenylproline (Fig. 1) features a proline skeleton that bears an aromatic group at the β carbon of the five-membered pyrrolidine ring. This proline analogue, which can be regarded as a proline–phenylalanine hybrid, is especially attractive because it combines the structural restrictions of proline[4] with a specifically-oriented aromatic side chain. Moreover, the stereochemical diversity of β-phenylproline, in which the phenyl group may exhibit either a *cis* or a *trans* orientation with respect to the carboxylic acid (Fig. 1), increases its potential as a tool for elucidating the conformational requirements for optimal peptide-receptor binding. Clearly, the utility of β-phenylproline to modulate peptide conformation relies on its ability to retain the conformational preferences of proline, which exhibits a high tendency to

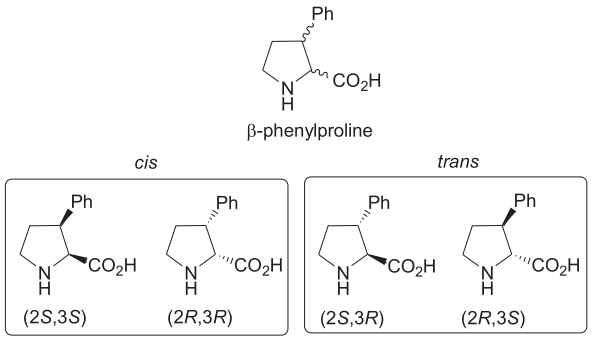

Fig. 1. Structure of the different stereoisomers of β-phenylproline. Note that positions 2 and 3 correspond, respectively, to the α and β carbons.

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http://dx.doi.org/10.1016/j.tet.2012.09.069

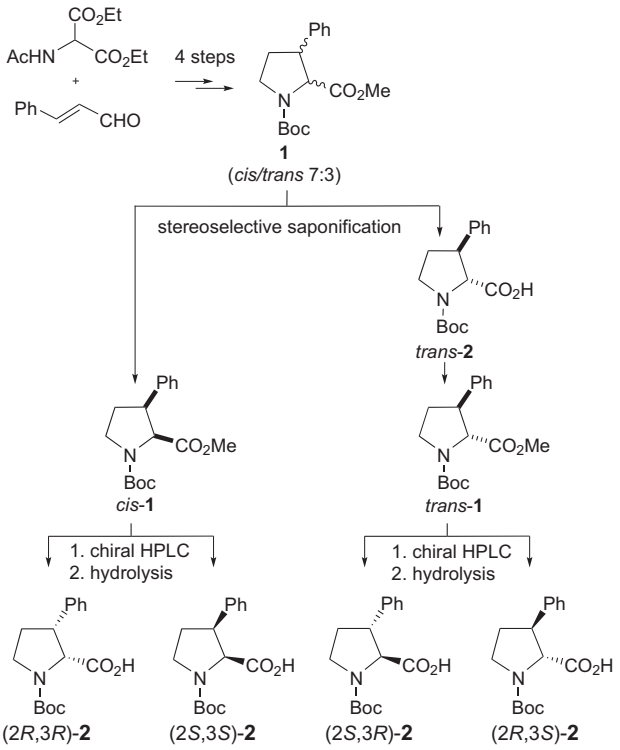
induce turns and, in particular, to occupy the $i+1$ position of β-turns.[4] In this regard, we have recently studied the conformational propensities of the *cis* and *trans* stereoisomers of β-phenylproline,[6] and shown that they retain the ability of the natural amino acid to induce β-turns. Moreover, the additional aromatic substituent may participate in aromatic interactions that increase the stability of the β-turn conformation.[6]

Several stereoisomers of β-phenylproline have been incorporated into a number of bioactive peptides.[3d,7] In particular, the (2*S*,3*R*) stereoisomer was used in structure-based design of selective inhibitors of caspase-2, which is a leading target for Huntington's disease.[7a] The same (2*S*,3*R*) stereoisomer afforded peptidomimetics that are resistant to hydrolytic cleavage, exhibit high binding affinity and are being studied as MHC-selective immunosuppressants for the treatment of rheumatoid arthritis and multiple sclerosis.[7b–d] In addition, several stereoisomers of β-phenylproline were employed to examine the role of a phenylalanine residue in the binding affinity of peptides for melanocortin,[7e] opioid[7f] or neurokinin[7g,h] receptors, or that of proline in the binding of α-conotoxins to nicotinic acetylcholine receptors.[7i]

The demonstrated value of β-phenylproline has stimulated the development of synthetic routes to access its different stereoisomers. Several methods that allow the preparation of one or more β-phenylproline stereoisomers in enantioenriched or optically pure form have been reported.[8] Some of them make use of L-proline or L-pyroglutamic acid (5-oxoproline) derivatives as chiral starting materials.[8a–c] Other routes are based on the cyclization of open-chain precursors bearing a chiral auxiliary.[8d–j] More recently, two procedures have been reported in which enantioselectivity is induced by an organocatalytic process.[8k,l] In spite of the variety of strategies available and their synthetic significance, a close analysis evidences that the efficiency of these procedures for the preparation of multigram quantities of (2*S*,3*S*)- and (2*S*,3*R*)-β-phenylproline (L-proline analogues) and the corresponding enantiomers is usually compromised by the accessibility to the highly elaborated starting precursors, the degree of stereocontrol achieved, the large number of synthetic steps or low overall yields. Moreover, some of the procedures obviate the analysis of the final compounds to determine the optical purity or this is assumed to be that of the starting chiral synthon.

On this basis, we searched for a more convenient methodology to gain access to all four stereoisomers of β-phenylproline in enantiomerically pure form and gram-scale quantities. As a result, we have recently described[9] a procedure based on the chromatographic resolution of racemic *N*-Boc-protected β-phenylprolinates of *cis* and *trans* stereochemistry (*cis*-**1** and *trans*-**1**, Scheme 1). Significant quantities (1.4–2.7 g) of each of the four stereoisomeric methyl *N*-Boc-β-phenylprolinates were thus obtained in optically pure form and subsequent deprotection of the ester function allowed the isolation of the corresponding enantiopure amino acids suitably protected for use in peptide synthesis[9] (Scheme 1).

The preparation of the racemic precursors to be resolved by HPLC methods (*cis*-**1** and *trans*-**1**)[9] followed a reported procedure[10] based on the formation of a *cis*/*trans* mixture of ethyl *N*-acetyl-β-phenylprolinates and their separation by selective saponification of the less hindered *trans* ester. However, we encountered difficulties in efficiently separating this mixture of isomers. Even if replacement of the acetyl by a Boc moiety and modification of the reaction conditions enhanced the selectivity of the saponification process,[9] a strict control of the experimental conditions is still necessary to ensure a clean separation of *cis*-**1** and *trans*-**2** (Scheme 1). This made us consider the convenience to develop new methods that would allow access to *cis*-**1** and *trans*-**1** in a selective manner, thus obviating the need for the separation of *cis*/*trans* isomers by saponification (note that these compounds are not separable by standard column chromatography on silica gel). We report herein a practical, highly stereoselective route for the efficient preparation

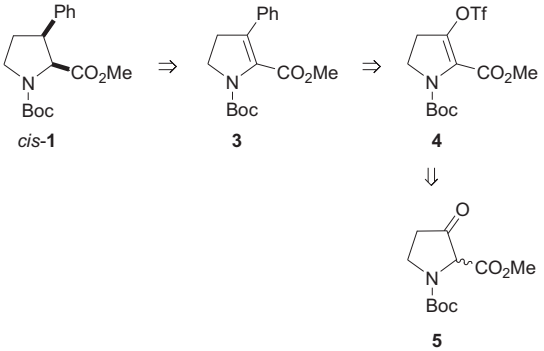


Scheme 1. Access to all *N*-Boc-β-phenylproline stereoisomers in enantiomerically pure form by HPLC resolution (polysaccharide-derived chiral columns) of racemic *cis*-**1** and *trans*-**1**, according to Ref. 9.

of the racemic β-phenylproline derivatives *cis*-**1** and *trans*-**1**, which have proven to be excellent precursors of the enantiopure *N*-Boc-amino acids (Scheme 1).[9]

2. Results and discussion

We envisioned that the 2,3-dehydroprolinate **3** (Scheme 2) could be a convenient precursor for the preparation of the desired *cis*-β-phenylproline derivative, *cis*-**1**, because the presence of a double bond connecting the α and β carbons would ensure a *cis* relative disposition of substituents upon hydrogenation. In turn, the synthesis of **3** could be achieved by means of a palladium-mediated cross-coupling reaction with phenylboronic acid. Vinyl triflate **4** (Scheme 2) was chosen as a convenient coupling partner[11] since a similar oxygen-based electrophile has previously been employed for the β-functionalization of proline by means of a Suzuki coupling.[8a] The projected vinyl triflate **4** could be generated from ketoproline **5**. The groups selected for protection of the amino and carboxylic acid functions in compounds **3**–**5** respond to our interest in developing a concise

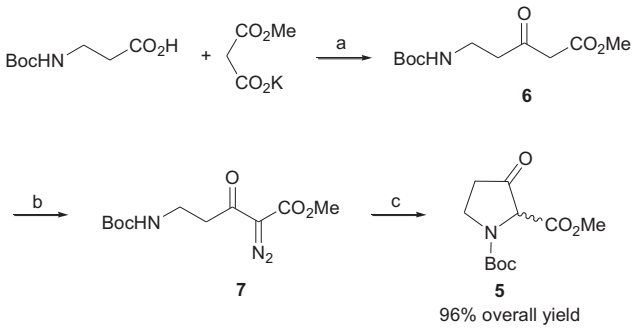


Scheme 2. Retrosynthetic route for the preparation of *cis*-**1**.

preparation of the target compound (*cis*-**1**). At the same time, they seem to be compatible with the type of synthetic transformations outlined above. It is clear that the stereoelectronic nature of such protecting groups will also be critical for the enolization process since a regioselective generation of **4** will be essential to achieve stereocontrol during the subsequent hydrogenation step.

In this context, two *N*-Boc-protected vinyl triflates with the desired double bond position have previously been reported in the literature.[12] Specifically, a vinyl triflate with a cyano group at C-2 of the pyrrolidine ring has been employed as a precursor for the preparation of *cis*-configured β-substituted proline carboxamides.[12a] More recently, Chen et al. described the use of an analogous vinyl triflate, namely the ethyl ester derivative, for the preparation of a variety of β-arylpyrrolidine-2-carboxamide derivatives to study their effect as melanocortin-4-receptor ligands.[12b] In the latter case, although the authors described that the vinyl triflate undergoes a cross-coupling reaction with phenylboronic acid in good yield, the *cis*-configured *N*-Boc-protected β-phenylproline was obtained in only 16% overall yield. This low yield was mainly due to an ineffective preparation of the required ketoproline by means of an intramolecular Dieckmann condensation followed by a triflation reaction. Indeed, the generation of 3-oxoproline derivatives by means of an intramolecular condensation of Dieckmann type, with potassium *tert*-butoxide in toluene at 0 °C, has been reported to occur in moderate yield due to the difficulty in achieving regiochemical control during the cyclization.[12b,13]

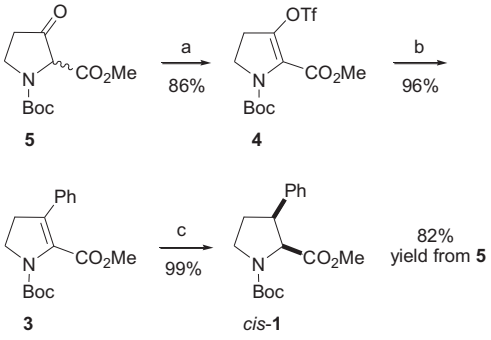
In view of this, we undertook a more efficient preparation of **5** starting from inexpensive, commercially available *N*-Boc-protected β-alanine. The desired ketoproline was prepared by means of an intramolecular N–H insertion reaction mediated by a metal carbenoid as the cyclization step (Scheme 3).[14] Firstly, the β-keto ester **6** was prepared through the modified Claisen reaction[14a] initially reported by Masamune.[15] Thus, the carbonyl group in β-alanine was activated with *N*,*N*′-carbonyldiimidazole and the resulting imidazolide was treated with a magnesium enolate generated under mild reaction conditions from the potassium salt of monomethyl malonate. The nucleophilic addition provided access to the β-keto ester **6** after a spontaneous decarboxylation occurring during the acidic workup.



Scheme 3. Synthesis of ketoproline **5** from *N*-Boc-β-alanine. Reagents and conditions: (a) *N*,*N*′-carbonyldiimidazole, $MgCl_2$, THF, rt; (b) 3-carboxybenzenesulfonyl azide, Et_3N, CH_3CN, rt; (c) $Rh_2(OAc)_4$, toluene, 85–90 °C.

The crude β-keto ester was subjected to a diazo transfer reaction employing 3-carboxybenzenesulfonyl azide, prepared as described by Sorensen et al.[14a] (Scheme 3). Similar results were obtained when using commercially available 4-acetamidobenzenesulfonyl azide for the diazo-transfer step. Although the resulting α-diazo-β-keto ester **7** is stable for purification by silica gel chromatography, there is no need for purification at this stage of the synthesis and the crude material was submitted to intramolecular cyclization. The N–H insertion reaction took place when compound **7** was decomposed by treatment with a catalytic amount of rhodium diacetate in toluene at 85–90 °C. The insertion occurs when the electrophilic metal carbenoid associated with the β-keto ester causes the cleavage of the N–H bond concurrent with the formation of the C–N and C–H bonds. The process cleanly delivered pure **5** in nearly quantitative yield after column chromatography purification. Thus, the synthetic route outlined in Scheme 3 provided multigram quantities of the desired ketoproline **5** in 96% overall yield, and involving a single purification step.

Next, the regioselective generation of vinyl triflate **4** was undertaken (Scheme 4). Treatment of ketoproline **5** with potassium bis(trimethylsilyl)amide as a base combined with triflic anhydride proved inefficient as the desired vinyl triflate (**4**) was isolated in very low yield (8–18%) from a complex mixture of products. This result is in contrast to that previously reported[12b,16] for the analogous ketoproline ethyl ester (KHMDS/THF, −78 °C, 30 min; then Tf_2O, room temperature, 2 h, 52%), and prompted us to test alternative triflating agents. The use of *N*-phenyltriflimide under the same reaction conditions afforded the desired vinyl triflate (**4**) contaminated with a side product that was tentatively identified as the regioisomeric vinyl triflate with a double bond between C-3 and C-4. Fortunately, trapping the enolate with *N*-(5-chloro-2-pyridyl) triflimide[17] provided **4** as the only regioisomer and in a reproducible 86% yield even when working on gram-scale quantities. The use of the latter triflimide with lithium bis(trimethylsilyl)amide as a base provided the inseparable mixture of triflates previously observed. Accordingly, the combination of potassium bis(trimethylsilyl)amide and *N*-(5-chloro-2-pyridyl)triflimide is essential to ensure complete regioselectivity in the formation of the desired vinyl triflate (**4**) and to allow its isolation in high yield.



Scheme 4. Synthesis of *cis*-**1** from ketoproline **5**. Reagents and conditions: (a) KHMDS, THF, −78 °C, 40 min; then *N*-(5-chloro-2-pyridyl)triflimide, THF, −78 °C to rt. (b) $PhB(OH)_2$, $PdCl_2(dppf)$, K_2CO_3, toluene/MeOH, 80–85 °C. (c) H_2, Pd/C, MeOH, rt.

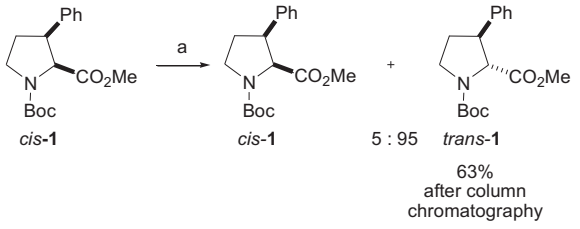
The vinyl triflate **4** was then submitted to a cross-coupling reaction to incorporate the phenyl substituent at the β position. Treatment of **4** with phenylboronic acid and potassium carbonate in the presence of a catalytic amount of [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium (II) provided **3** in high yield (Scheme 4).[12b] This reaction was carried out immediately after the chromatographic purification of **4** to avoid thermal decomposition.[18] Finally, the catalytic hydrogenation of **3** under standard conditions rendered *cis*-**1** as the only stereoisomer in nearly quantitative yield (Scheme 4).

Therefore, we have developed a methodology that provides access to the desired derivative of *cis*-β-phenylproline, *cis*-**1**, in high overall yield (78%), and through transformations that proceed with full stereochemical control. The route has been applied to the preparation of multigram quantities of *cis*-**1** and is amenable to larger-scale production, with only a few chromatographic purifications being necessary.

The epimerization of *cis*-**1** would represent a very concise way to access the *trans* stereoisomer. Actually, treatment of a *cis*/*trans*

mixture of ethyl *N*-acetyl-β-phenylprolinates with sodium ethoxide in ethanol has been reported to increase the percentage of the initially minor *trans* isomer to about 70%.[10] However, as commented above, a selective saponification process is required to separate the mixture of isomers, since the ca. 30% of *cis* ester remaining in the epimerized mixture makes unfeasible their separation by standard chromatographic procedures.

This situation prompted us to study the epimerization of *cis*-**1**. The use of sodium alkoxides for this purpose did not improve significantly the results previously reported[10] for the epimerization of *cis*/*trans* mixtures of ethyl *N*-acetyl-β-phenylprolinates. In contrast, treatment of *cis*-**1** with excess lithium bis(trimethylsilyl)amide at room temperature for 2 h cleanly afforded a 5:95 ratio of *cis*-**1**/*trans*-**1**, from which the *trans* isomer was isolated pure in 63% yield after column chromatography (Scheme 5). Increase of this yield by extensive chromatographic purification was not attempted. For large-scale production, the most practical approach to increase the final yield of pure *trans*-**1** would certainly be epimerization of the remaining *trans*-enriched mixture to regain a 5:95 *cis*/*trans* ratio prior to further chromatographic separation. In fact, isolation of pure *trans* isomer by routine chromatographic procedures is only possible when small percentages of the *cis* isomer remain in the mixture.



Scheme 5. Epimerization of *cis*-**1** to give *trans*-**1**. Reagents and conditions: (a) 1. LiHMDS, THF, rt; 2. H_2O.

3. Conclusion

A very efficient methodology for the preparation of methyl *cis*-*N*-Boc-β-phenylprolinate employing β-alanine as the starting material has been developed. Completely regio- and stereoselective high-yielding transformations have allowed the isolation of this *cis*-β-phenylproline derivative in 78% overall yield. In turn, this compound furnished the corresponding *trans* stereoisomer through an epimerization process. The high stereoselectivity achieved during the epimerization allowed the isolation of the *trans*-β-phenylproline derivative by standard chromatographic procedures. The procedure has been applied to the synthesis of gram quantities of the target β-phenylprolinates and is amenable to larger-scale production. The β-phenylproline derivatives prepared have been shown to be excellent precursors of the enantiopure *N*-Boc amino acids.[9] The new synthetic route developed circumvented the need for the separation of *cis*/*trans* isomers by selective saponification, as required in the procedure previously reported for these β-phenylproline derivatives.[9]

4. Experimental

4.1. General

All reagents were used as received from commercial suppliers without further purification. Thin-layer chromatography (TLC) was performed on Macherey–Nagel Polygram® SIL G/UV$_{254}$ precoated silica gel polyester plates. The products were visualized by exposure to UV light, iodine vapour or an ethanolic solution of phosphomolybdic acid. Column chromatography was performed using 60 M (0.04–0.063 mm) silica gel from Macherey–Nagel. Melting points were determined on a Gallenkamp apparatus. IR spectra were registered on a Nicolet Avatar 360 FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 instrument at room temperature using the residual solvent signal as the internal standard; chemical shifts (δ) are expressed in parts per million and coupling constants (J) in hertz. High-resolution mass spectra were obtained on a Bruker Microtof-Q spectrometer.

4.2. Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-3-oxopyrrolidine-2-carboxylate, 5

A solution of *N*-(*tert*-butoxycarbonyl)-β-alanine (6.00 g, 31.71 mmol) in anhydrous tetrahydrofuran (100 mL) under an argon atmosphere was treated with *N*,*N*′-carbonyldiimidazole (7.24 g, 38.05 mmol). After stirring at room temperature for 1 h, previously mixed magnesium chloride (3.00 g, 31.51 mmol) and monomethyl monopotassium malonate (9.84 g, 63.02 mmol) were added. The resulting mixture was kept under an argon atmosphere and was stirred at room temperature for an additional 18 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (100 mL) and washed with 5% aqueous $KHSO_4$ (2×50 mL), 5% aqueous $NaHCO_3$ (2×50 mL) and brine (2×50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford **6** as a pale yellow oil (7.70 g, 31.39 mmol). The crude compound was dissolved in anhydrous acetonitrile (100 mL), under an argon atmosphere, and 3-carboxybenzenesulfonyl azide (7.84 g, 34.53 mmol) was added in one portion, followed by triethylamine (13.13 mL, 94.17 mmol). The resulting mixture was stirred at room temperature for 1 h. The solvent was concentrated in vacuo and the residue was dissolved in diethyl ether (100 mL) and washed with saturated aqueous $NaHCO_3$ (2×50 mL), and saturated aqueous NH_4Cl (2×50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford **7** as an orange oil (8.35 g, 30.78 mmol) that was taken on without further purification. It was dissolved in anhydrous toluene (300 mL), under an argon atmosphere, and $Rh_2(OAc)_4$ (0.068 g, 0.15 mmol) was added. The reaction mixture was heated at 85–90 °C for approximately 30 min in a preheated oil bath. The solvent was evaporated to dryness and the residue was purified by column chromatography (eluent: hexanes/ethyl acetate 3:1) to afford pure **5** as a white solid (7.41 g, 30.47 mmol, 96% overall yield). Mp 56 °C. IR (neat) ν 2979, 1772, 1745, 1707 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39, 1.46 (two s, 9H), 2.59–2.76 (dd, 2H, J=8.4, 6.8 Hz), 3.66–3.94 (m, 5H), 4.46, 4.54 (two s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (duplicate signals are observed for most carbons) 28.09, 28.19; 36.37, 37.06; 41.52, 42.17; 52.86, 53.00; 65.20, 65.60; 81.15; 153.75; 166.69; 204.52. HRMS (ESI) $C_{11}H_{17}NNaO_5$ $[M+Na]^+$: calcd 266.0999, found 266.1004.

4.3. Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-3-trifluoromethanesulfonyl-Δ^2-pyrroline-2-carboxylate, 4

A 0.5 M solution of KHMDS in toluene (77.70 mL, 38.85 mmol) was added by syringe to a stirred solution of **5** (6.30 g, 25.90 mmol) in anhydrous tetrahydrofuran (190 mL) cooled at −78 °C. After 40 min stirring, *N*-(5-chloro-2-pyridyl)triflimide (12.20 g, 31.08 mmol) was added. The cooling bath was removed and the solution was allowed to stir for an additional 4 h while warming up to room temperature. The solvent was evaporated to dryness and the residue was purified by column chromatography (eluent: hexanes/ethyl acetate 6:1) to afford pure **4** as a light yellow oil (8.36 g, 22.27 mmol, 86% yield). IR (neat) ν 2981, 1750, 1716, 1429, 1407, 1370, 1324, 1216, 1139, 1030, 989 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 2.94 (m, 2H), 3.86 (s, 3H), 3.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.13, 28.93, 46.22, 52.72, 82.60, 113.62,

116.81, 120.00, 123.18, 128.30, 137.87, 152.41, 159.66. HRMS (ESI) $C_{12}H_{16}F_3NNaO_7S$ $[M+Na]^+$: calcd 398.0492, found 398.0494.

4.4. Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-3-phenyl-Δ^2-pyrroline-2-carboxylate, 3

To a solution of **4** (7.20 g, 19.18 mmol) and phenylboronic acid (4.68 g, 38.36 mmol) in a 10:1 mixture of toluene/methanol (154 mL), potassium carbonate (4.00 g, 28.94 mmol) and [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (700 mg, 0.96 mmol) were added. The reaction mixture was stirred at 80–85 °C for 18 h. The solvent was concentrated in vacuo and the resulting residue was purified by silica gel column chromatography (eluent: hexanes/ethyl acetate 4:1) to afford pure **3** as a white solid (5.60 g, 18.46 mmol, 96% yield). Mp 66 °C. IR (neat) ν 2978, 1739, 1701, 1627 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 3.04 (m, 2H), 3.83 (s, 3H), 3.97 (m, 2H), 7.22–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.38, 32.25, 46.68, 52.53, 81.55, 126.47, 127.66, 128.51, 129.74, 133.88, 151.93, 164.49. HRMS (ESI) $C_{17}H_{21}NNaO_4$ $[M+Na]^+$: calcd 326.1363, found 326.1358.

4.5. Synthesis of methyl *cis*-*N*-(*tert*-butoxycarbonyl)-3-phenylpyrrolidine-2-carboxylate, *cis*-1

A mixture of **3** (5.60 g, 18.46 mmol) and 10% Pd/C (600 mg) in methanol (56 mL) was stirred overnight at room temperature under an atmospheric pressure of hydrogen gas. The catalyst was filtered off and washed with methanol. The solvent was concentrated in vacuo to afford pure *cis*-**1** as a white solid (5.60 g, 18.34 mmol, 99% yield). Spectroscopic data were coincident with those reported.[9]

4.6. Synthesis of methyl *trans*-*N*-(*tert*-butoxycarbonyl)-3-phenylpyrrolidine-2-carboxylate, *trans*-1

A 1 M solution of LiHMDS in tetrahydrofuran (14.73 mL, 14.73 mmol) was added dropwise to a solution of *cis*-**1** (3.00 g, 9.82 mmol) in tetrahydrofuran (80 mL) and the resulting mixture was stirred for 2 h at room temperature. After quenching with water, the mixture was extracted with diethyl ether (3×50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude 5:95 mixture of *cis*/*trans* isomers was submitted to column chromatography (eluent: hexanes/ethyl acetate 3:1) to afford pure *trans*-**1** (1.90 g, 6.22 mmol, 63% yield); further chromatographic purification of the remaining diastereomeric mixture to increase the isolated yield of *trans*-**1** was not carried out. Spectroscopic data were coincident with those reported.[9]

Acknowledgements

The authors thank the Ministerio de Ciencia e Innovación–FEDER (grant CTQ2010-17436; FPI fellowship to I.R.) and Gobierno de Aragón–FSE (research group E40) for financial support.

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