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A Selective Deprotection Strategy for the Construction of *trans*-2-Aminocyclopropanecarboxylic Acid Derived Peptides

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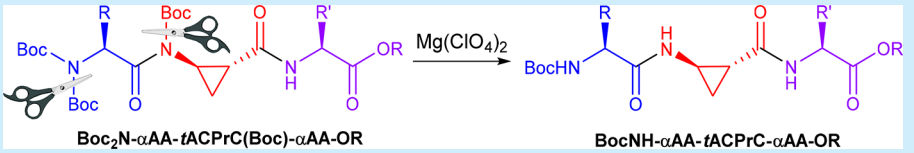
Supporting Information



ABSTRACT: A procedure allowing access to unprecedented tripeptides containing a *trans*-2-aminocyclopropanecarboxylic acid residue in their central position has been established. The key features of the strategy are the use of a masked *trans*-2-aminocyclopropanecarboxylic acid monomer equivalent for C-terminal coupling and full N-Boc protection of all amide groups until the final step.

Carbocyclic β-amino acids are an important molecular class whose structures appear in natural products and pharmacologically active molecules.[1] They have also been used ubiquitously as building blocks for the construction of peptidic foldamers.[2] Consequently, various methodologies have been established for the selective synthesis of such compounds.[3] Within this family, 2-aminocyclopropanecarboxylic acid (ACPrC) represents a special case: the free amino acid has never been described because its high ring strain coupled with the vicinal donor−acceptor substituent profile induces rapid and irreversible ring opening, in a retro-Mannich type reaction (Figure 1).[4]

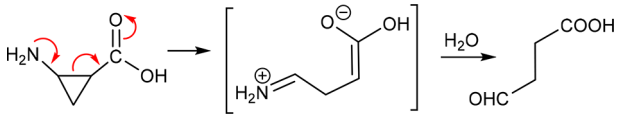


Figure 1. ACPrC core structure and its inherent ring opening reactivity.

The preparation of ACPrC derivatives is therefore a considerable challenge, for which a number of approaches have been investigated.[5,6] Syntheses of protected derivatives of the *trans* isomer (*t*ACPrC) have been achieved via desymmetrization of *trans*-cyclopropane-1,2-dicarboxylates followed by Curtius rearrangement,[7] ring closure of β-amino-γ-iodobutyrates,[8] substitution of β-bromocyclopropanecarboxamides,[9] or asymmetric cyclopropanation of vinylamide derivatives.[10] Approaches to the synthesis of protected derivatives of the *cis* isomer (*c*ACPrC) are more limited.[7c,10b,11] Stable ACPrC derivatives which have been prepared to date are presented in Figure 2. It is significant that in all these compounds, the amine invariably bears an electron-withdrawing group that serves to suppress the deleterious ring opening reaction.

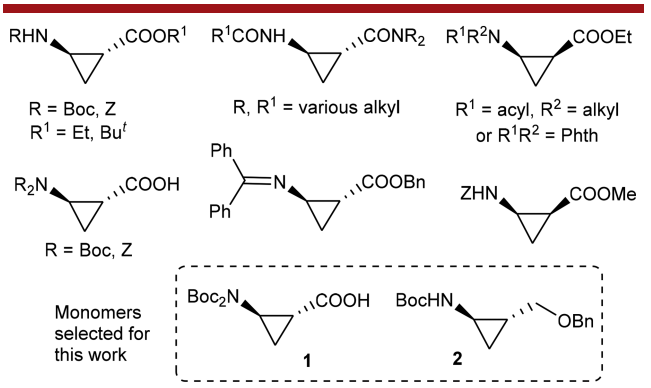


Figure 2. Previously described nonracemic ACPrC derivatives and the derivatives used in this work.

Given these stability problems, peptides incorporating ACPrC residues are extremely rare. Reiser found that an extra carboxylate group at the cyclopropane 3-position stabilized the *c*ACPrC core sufficiently to facilitate the preparation of short peptides, some of which displayed biological activity,[12] organocatalytic activity,[13] and foldamer propensity.[14] These reports demonstrate the considerable potential of ACPrC peptides; however, procedures for the preparation of peptides containing unsubstituted ACPrC residues are severely limited. North was able to desymmetrize *cis*-cyclopropane-1,2-dicarboxylic anhydride using proline followed by a Curtius rearrangement, to afford a urea-based

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pseudopeptide incorporating *c*ACPrC, as well as a carbamate protected dipeptide, Teoc-*c*ACPrC-Pro-OBu^t. However, efforts to deprotect the latter resulted in complete degradation.[15] Mangelinckx and De Kimpe used the *N*-diphenylmethylidene (DPM) derivative of *t*ACPrC to prepare the dipeptide DPM-*t*ACPrC-Gly-OMe, but once again reaction of the N-terminus was precluded.[8] Therefore, there is currently no viable procedure for the construction of peptides which include unsubstituted ACPrC as an internal or C-terminal residue.[16]

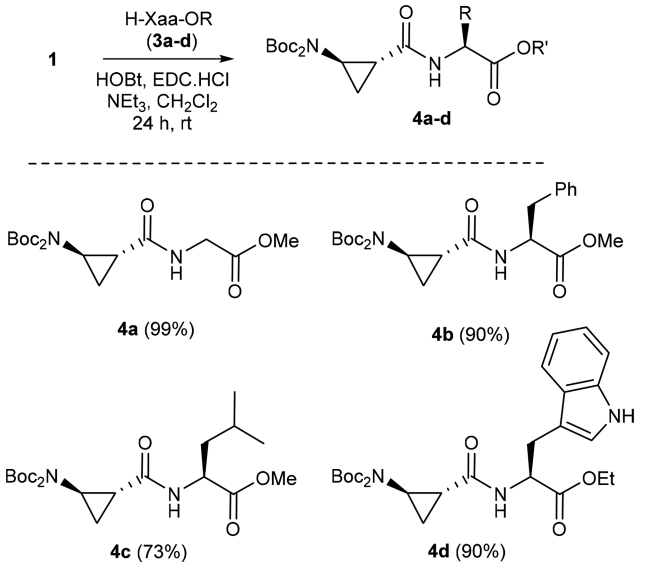
We decided to address this deficiency and elaborate a protocol which would allow access to a tripeptide containing *t*ACPrC as the internal residue. For this endeavor, the choice of monomer building blocks was critical: while the doubly protected derivative **1** appeared a good choice as a C-terminal coupling partner, none of the *t*ACPrC derivatives in Figure 1 seemed likely to tolerate N-deprotection without ring opening. For this reason, we selected a masked *t*ACPrC derivative, compound **2**, as a key building block (Figure 2). We envisaged that Boc removal and then N-coupling should be straightforward, since there would be no risk of ring opening of the vicinal benzyloxymethyl substituent. Thereafter, oxidation of the deprotected primary alcohol would provide the free acid for C-terminal coupling. Compound **2** was readily available in three steps starting from (*S*)-glycidol benzyl ether,[17] and it also served as a convenient precursor for compound **1** using the three-step procedure of Vederas,[18] which involves introduction of a second Boc group, debenzylation, and oxidation (see Supporting Information). Protection of the amine as its di-Boc derivative was essential for the success of the oxidation step, since degradation occurred when only one Boc group was present. Catalytically generated ruthenium tetroxide conditions were chosen for the oxidation step, because these conditions had been used previously for the successful oxidation of related cyclopropyl alcohols to their corresponding acids.[19]

Our first objective was to prepare dipeptides of general structure Pg-*t*ACPrC-Xaa-OR. Coupling of **1** with each of four standard α-amino esters **3a**–**d** was carried out using 1-(3-(dimethylamino)propyl)-3-ethyl carbodiimide hydrochloride (EDCI·HCl) and 1-hydroxybenzotriazole hydrate (HOBt·H_2O) in the presence of triethylamine in dichloromethane for 24 h. The corresponding dipeptides **4a**–**4d** were obtained in good to excellent yields (73–99%) and proved to be stable (Scheme 1).

Dipeptide **4d** gave crystals which were suitable for X-ray diffraction analysis (CCDC 1841687, Figure 3). To the best of our knowledge, solid state structural data for *t*ACPrC derivatives have not been reported previously. As well as confirming the (1*R*,2*R*) absolute configuration, the crystal structure revealed a very large dihedral angle (N–Cβ–Cα–CO) of −138.01°, which was considerably greater than the corresponding value (around 96°) for *trans*-cyclobutane-β-amino acid derivatives.[20]

We then turned our attention to the more challenging preparation of dipeptides of general structure Pg-Xaa-*t*ACPrC-OH, for which the requisite monomer was compound **2**. It was reasoned that the most convenient way to carry out deprotection of **2** was to treat it with TFA and use the resultant ammonium salt directly in coupling reactions. Therefore, compound **2** was treated with an excess of TFA in dichloromethane for 2 h, and the resulting salt **5** coupled (EDCI·HCl, HOBt·H_2O, Et_3N, dichloromethane) with two representative *N*-Boc-protected α-amino acids **6a** and **6b**, which were selected for their low and high degrees of steric

Scheme 1. Coupling of *t*ACPrC 1 at the C-terminal



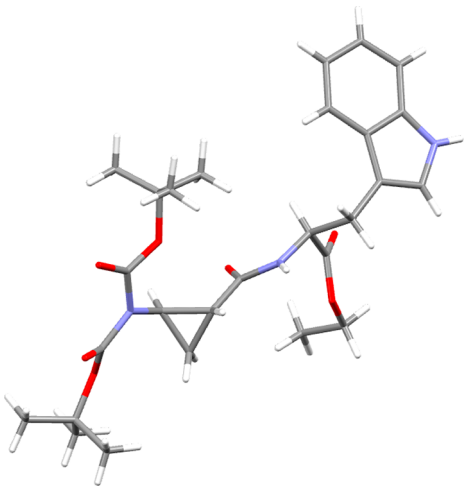


Figure 3. X-ray diffraction structure of compound **4d**.

hindrance, respectively. The corresponding derivatives **7a** and **7b** were obtained in high 86% and 87% yields, respectively (Scheme 2).

Considering that the transformation of monomer **2** into monomer **1** required double Boc-protection of the amine, we took the same precaution during the C-terminal oxidation steps that were conducted on derivatives **7a** and **7b**. Use of a large excess of di-*tert*-butyl dicarbonate (Boc_2O) and a catalytic amount of DMAP enabled a second *tert*-butyl carbamate group to be introduced onto the nitrogen atoms of **7a** and **7b**, providing **8a** and **8b** in good 73% and 84% yields, respectively (Scheme 2). Each of these compounds was debenzylated by hydrogenolysis to give **9a** and **9b** in near-quantitative yield. Gratifyingly, oxidation of **9a** gave glycyl dipeptide **10a** in an excellent 93% yield. However, oxidation of **9b** gave pyroglutamyl dipeptide **10b** as the major product in 65% yield, along with the anticipated prolyl dipeptide **10c** in 17% yield. Ruthenium tetroxide mediated oxidation of protected prolyl residues and pyrrolidine systems has been reported previously,[21,22] competing formation of the pyrrolidinone ring of **10b** suggests a limitation of this oxidative methodology. All

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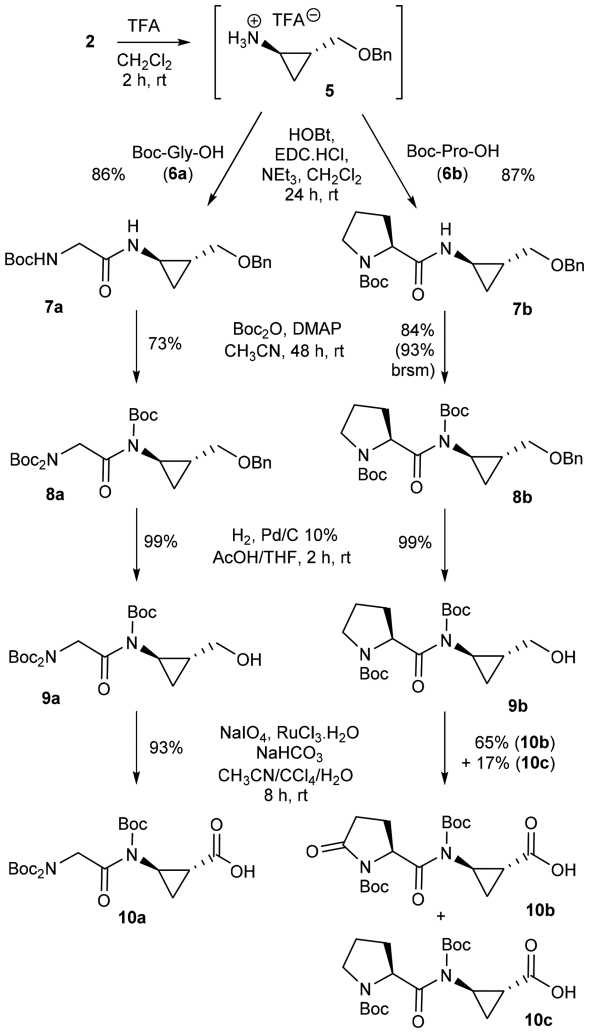
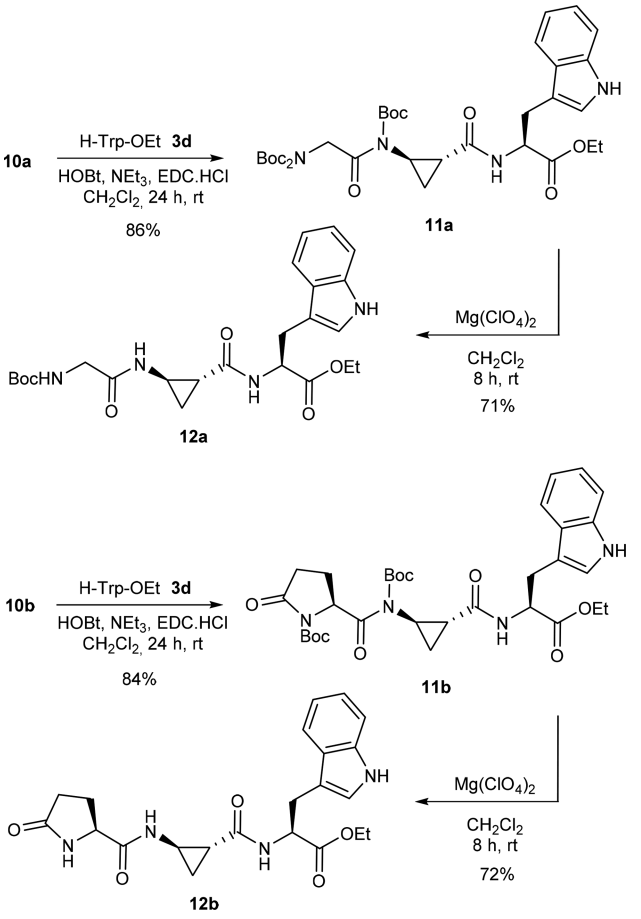
Scheme 2. Coupling of Masked *t*ACPrC 5 at the N-Terminal



Scheme 3. Synthesis of Tripeptides 12a and 12b



three derivatives **10a−c** proved to be stable dipeptides featuring an unprotected *t*ACPrC at their C-terminals.

The final challenge was to prepare a tripeptide system of the type Pg-Xaa-*t*ACPrC-Xaa-OR. Both dipeptides **10a** and **10b** were activated (EDCI·HCl, HOBt·H_2O, Et_3N, dichloromethane) and coupled with tryptophan ethyl ester **3d**. The corresponding tripeptides **11a** and **11b** were obtained in good 86% and 84% yields, respectively (Scheme 3). The final deprotection step was crucial, requiring removal of the internal Boc group to reveal an amide bond, while maintaining the terminal amine N-Boc group to avoid the unwanted ring opening process. We chose not to use a Brønsted acid (TFA, or $HCl_{(aq)}$) because these conditions would be likely to induce full deprotection of all the N-Boc groups of **11a**. Consequently, we sought to identify a suitable Lewis acid that would enable selective deprotection. Treatment of **11a** with lithium bromide in acetonitrile was ineffective at room temperature and induced rapid degradation upon heating. However, prompted by the methodology developed by Martin,[23] we found that treatment of **11a** with magnesium perchlorate in dichloromethane at room temperature allowed selective cleavage of two out of the three N-Boc groups, affording the N- and C-terminal protected tripeptide **12a** in 71% yield. These conditions were then applied to compound **11b**, providing access to the globally deprotected tripeptide **12b** in 72% yield (Scheme 3). These target compounds were sufficiently stable to be purified by standard column chromatography on silica gel and could be stored for several months at −18 °C without any visible degradation.

In summary, we have demonstrated a viable strategy for the preparation of di- and tripeptides that contain the elusive *β*-amino acid *t*ACPrC as a central unit. While the monomer itself is inherently unstable, stable peptides can be constructed using appropriately masked derivatives, with the deprotected residue being revealed after suitable peptide coupling reactions have been carried out. This approach should, in principle, be applicable for the syntheses of other *t*ACPrC derived peptides of different lengths and composition.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03533.

Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1841687 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam-

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Notes

The authors declare no competing financial interest.

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