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Synthesis of Trishomocubane Amino Acid Derivatives

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ABSTRACT

The synthesis of four novel trishomocubane amino acid derivatives is described. The hydantoin precursor and bis-Boc protected hydantoin (>95% yield) were previously reported. A mild hydrolysis of the bis-Boc hydantoin with lithium hydroxide at room temperature quantitatively yielded the corresponding novel cage amino acid. The cage amino acid was characterized as the Fmoc derivative. Although the Fmoc amino acid is partially deprotected after three weeks in a refrigerator, it is stable enough for use in Solid Phase Peptide Synthesis (SPPS). The Fmoc cage amino acid was converted to the acid fluoride with cyanuric fluoride. The acid fluoride is required for activation of the cage amino acid in SPPS. Esterification of the sterically hindered trishomocubane amino acid is also reported, indicating sufficient reactivity of the acid function for potential use in SPPS.

KEYWORDS

Trishomocubane amino acid, hydantoin, Fmoc protection, t-Boc protection, acid fluoride, esterification.

1. Introduction

Cage amino compounds have promising potential as an important new class of medicinal and pharmaceutical agents and might extend the existing range[1] of bio-active amino cage compounds. The incorporation of cage molecules into various peptide drugs has proven to aid biological activity.[2] As part of a programme to synthesize novel cage amino acids the pentacyclo-undecane-derived cage amino acids (–)–**1** and (+)–2 were recently reported (see Fig. 1).[3]

A logical extension of the previous research is to utilize the same method[4] on trishomocubanone (**3**)[5] to obtain the novel trishomocubane amino acid (**5**) (see Scheme 1).

Computational studies[6,7] in our laboratory indicated that the cage skeletons (**1** as well as **5**) have the tendency to impose a 3_{10}-helix as well as an α_L-helix on the polypeptide chain. Non-natural residues (such as **1** and **5**) are useful tools for the study of the conformational preferences of their models, the design of peptide analogues with improved pharmacokinetic profiles and the development of pharmacophore models.[8] Synthesis of trishomocubane amino acid analogues suitable for peptide synthesis would enable us to verify the computational predictions and to contribute to this very active field of research.

Trishomocubane is a chiral molecule with unusual symmetry.[9–11] The D_3 symmetry[5b] of the cage ensures that only two enantiomers are formed due to substitution at the quaternary substituted carbon (C_4, see Fig. 2), instead of the usual set of four diastereomers, as was potentially the case with the pentacyclo-undecane analogues **1** and **2**.

This unique symmetry of the trishomocubane skeleton makes it an even more attractive substrate in amino acid synthesis since no diastereomers will be formed.

2. Experimental

Infrared spectra (KBr-disc) were recorded on a Nicolet 5DX FT-spectrophotometer. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt, University of Texas at Austin using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. The fast atom bombardment (FAB) mass spectra were obtained from a Micromass VG70-70E mass spectrometer, equipped with an In Tech FAB gun at Potchefstroom University. The samples were bombarded with xenon atoms (1 mA at 8 keV), with *m*-nitrobenzyl alcohol as the matrix. Melting points are uncorrected. NMR spectra were recorded on a Varian Unity Inova-400 MHz spectrometer. The same numbering system as presented in Fig. 4 was used for presentation of the NMR data.

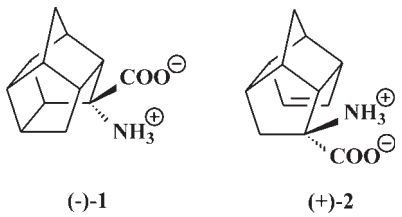

Figure 1 Pentacyclo-undecane derived amino acids.[3]

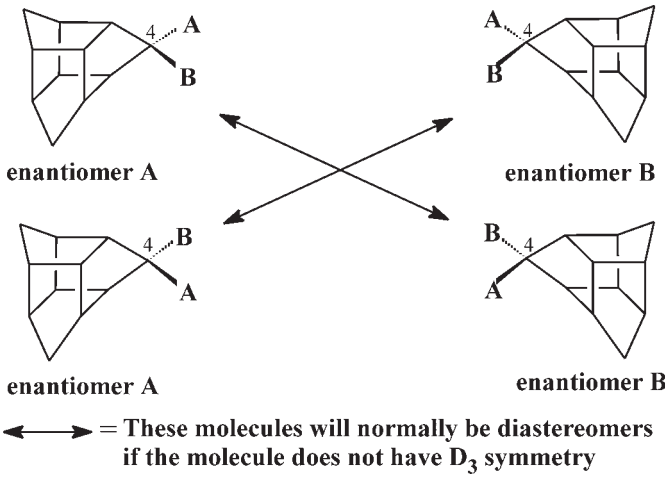

Figure 2 'Diastereomers' of the quaternary substituted carbon of trishomocubane.

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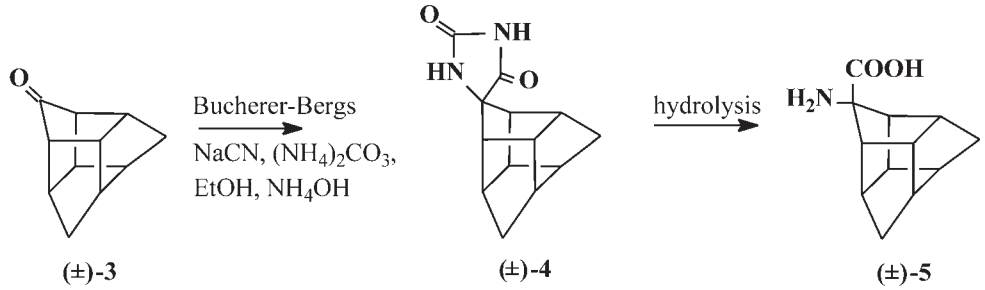

Scheme 1 Synthesis of the trishomocubane amino acid.

*4-Amino-(D_3)-trishomocubane-4-carboxylic Acid (**5**)*

The procedure was adapted from the literature,[13] The bis-Boc derivative (**7**)[12] in aqueous LiOH (8 mol equivalents) was stirred in a round bottom flask overnight. The resulting solution was adjusted to pH 6.5 using conc. HCl. The trishomocubane amino acid (**5**) precipitated from solution and was filtered off to remove the water and by-products. The product (**5**, >95%) was washed with acetone and diethyl ether. The amino acid was characterized as the Fmoc derivative (**8**).

*Synthesis of Fmoc-tris-amino Acid (**8**)*

The procedure was adapted from the literature.[15] To an ice-cooled solution of amino acid (**5**, 0.10 g, 4.88×10^{-4} mol) in dioxane (7.5 mL) and 10% (%$_v$) Na_2CO_3 (20 mL) was added, with stirring, a solution of 9-fluorenylmethyl chloroformate (Fmoc, 0.15 g, 5.80×10^{-4} mol) in dioxane (5.0 mL). This was left to stir in the ice-bath for four hours and then at room temperature for a further eight hours. The solution was diluted with deionized water (50 mL) and extracted with diethyl ether (100 mL). The aqueous layer was cooled to 10°C in an ice-bath and acidified to pH 2 with concentrated HCl. The solution was subsequently extracted with ethyl acetate (150 mL). The ethyl acetate layer was evaporated *in vacuo* to give the crude Fmoc derivative (**8**). Purification was achieved through silica gel column chromatography (dichloromethane) as well as recrystallization from dichloromethane and hexane (**8**, 0.16 g, 75%). m.p. 213°C. IR (KBr): υ_{max} 3360, 2952, 1748, 1702, 1294 cm^{-1}. ^{1}H NMR [DMSO, 400 MHz]: δ_H1.15–1.50 (m, 4H), 1.90–2.30 (m, 7H), 2.30–2.40 (m, 1H), 3.35 (s, 1H, D_2O exchangeable), 4.10–4.43 (m, 3H), 7.22–8.08 (m, 8H), 12.17 (s, 1H, D_2O exchangeable). ^{13}C NMR [DMSO, 100 MHz]: δ_C 31.7 (t), 32.7 (t), 42.5 (d), 42.6 (d), 42.8 (d), 43.8 (d), 46.1 (d), 46.4 (d), 46.7 (d), 52.8 (d), 53.3 (d), 65.1 (s), 68.6 (t), 120.0 (d), 125.1 (d), 125.2 (d), 126.9 (d), 127.9 (d), 140.6 (s), 140.7 (s), 143.7 (s), 143.8 (s), 155.3 (s), 174.0 (s). CI MS: Calc. for $C_{27}H_{26}NO_4$ $[M+H]^+$ m/z 428.1862, Found 428.1860. Anal. Calc. for $C_{27}H_{25}NO_4$: % C 75.86, % H 5.89, % N 3.28; Found % C 75.95, % H 5.95, % N 3.30.

*Synthesis of Fmoc Trishomocubane Acid Fluoride (**9**)*

The procedure was adapted from the literature.[21,27] Cyanuric fluoride (40.5 μL, 4.68×10^{-4} mol) was added to a suspension of Fmoc-tris-amino acid (**8**, 0.20 g, 4.68×10^{-4} mol) and dry dichloromethane (50 mL). Dry pyridine was subsequently added (37.8 μL, 4.6810^{-4} mol) and the resulting solution was left to stir under nitrogen for 12 hours. The mixture, which contained a white suspension of water-soluble cyanuric acid was further diluted with ice water (40 mL). The organic phase was dried over $MgSO_4$, filtered and subsequently removed *in vacuo*. The resulting white solid was recrystallized from dichloromethane/hexane to give the pure acid fluoride as a white solid (**9**, 0.17 g, 87%). m.p. 85°C. IR (KBr): υ_{max} 3346, 2966, 1829, 1724, 1504, 1457, 1277 cm^{-1}; ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 1.16–1.18 (m, 4H), 1.96–2.46 (m, 7H), 2.73 (br s, 1H), 4.22 (t, *J* 6.4 Hz, 1H), 4.75 (d, *J* 6.4 Hz, 2H), 5.38 (s, 1H, D_2O exchangeable), 7.25–7.48 (m, 4H), 7.59 (d, *J* 7.0 Hz, 2H), 7.77 (d, *J* 7.0 Hz, 2H). ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 32.0 (t), 33.0 (t), 42.7 (d), 42.9 (d), 43.2 (d), 44.2 (d), 46.9 (d), 47.0 (d), 47.2 (d), 53.7 (d), 54.1 (d), 66.7 (t), 68.8 (d, *J* 82.5 Hz, C_4), 119.3 (d), 124.8 (d), 127.0 (d), 127.6 (d), 141.3 (s), 143.5 (s), 155.2 (s), 162.3 (d, *J* 555 Hz, $C_{2'}$). ^{19}F NMR [$CDCl_3$, 400 MHz]: δ_F 234.1. CI MS: Calc. for $C_{27}H_{24}FNO_3$ $[M+H]^+$ m/z 429.1740, Found 429.1742.

*Ethyl Ester of the Trishomocubane Amino Acid (**10**)*

The procedure was adapted from literature.[28] A solution of trishomocubane amino acid **5** (0.41 g, 2.00×10^{-3} mol) in ethanol was treated with thionyl chloride (0.50 mL, 6.85×10^{-3} mol) and heated under reflux for 24 hours. The solution was evaporated to dryness under reduced pressure to yield the crude product. Deionized water was added to the crude mixture and the ester was extracted with dichloromethane. The organic solvent was removed *in vacuo* to yield the amino acid ester, which was purified by silica gel chromatography (dichloromethane) to yield a pure white wax (**10**, 0.33 g, 71%). m.p. 56°C. IR (KBr): υ_{max} 3427, 2954, 2869, 1730 cm^{-1}. ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 1.25–1.28 (t, 3H, $H_{5'}$, 6.7 Hz), 1.30 (m, 2H, H_{7s}, H_{11s}), 1.37–1.39 (d, H_{11a}, *J* 11.7 Hz), 1.39–1.42 (d, H_{7a}, *J* 11.7 Hz), 1.80 (s, $H_{1'}$, D_2O exchangeable protons), 1.94–1.95 (br s, H_3), 2.07–2.10 (m, H_5), 2.10–2.11 (m, H_1, H_8, $H_{10'}$), 2.12–2.15 (m, H_9), 2.15–2.18 (m, H_2), 2.60 (m, H_6), 4.12–4.18 (q, $H_{4'}$). ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 14.2 ($C_{5'}$), 32.7, 33.6 (C_7, C_{11}), 42.1 (C_2), 43.2 (C_{10}), 44.6 (C_6), 46.9, 46.9 (C_1, C_8), 54.0 (C_5), 56.2 (C_3), 60.5 ($C_{4'}$), 69.1 (C_4), 175.7 ($C_{2'}$). M.S. $[M+H]^+$ 234 m/z. Anal. Calc. for $C_{14}H_{19}NO_2$: % C 72,07, % H 8.21, % N 6.00; Found % C 71,95, % H 8.07, % N 5.88.

3. Results and Discussion

The trishomocubane hydantoin (**4**) and bis-Boc protected hydantoin (**7**, >95% yield) were synthesized as before.[12] Rebek's method[13] of hydrolysis of the hydantoin ring was applied to the bis-Boc hydantoin (**7**) and the corresponding novel trishomocubane amino acid (**5**) was obtained in nearly quantitative yield which is a useful improvement on conventional hydrolysis[3,14] of the unprotected hydantoin. Adjustment of the pH to 6.5 resulted in precipitation of the amino acid (**5**). The trishomocubane amino acid (**5**) was characterized through the Fmoc[15] derivative (**8**) and the ethyl ester (**10**) described below. (Fig. 3)

Recrystallization of **8** from dichloromethane and hexane provided a product for which the CI mass spectrum exhibits a molecular ion at m/z 428, confirming the formation of the desired Fmoc-protected amino acid. A ninhydrin test (Kaiser test)[16] was used to confirm the absence of any primary amines. The infrared spectrum shows absorption at 3358 and 1710 cm^{-1} for the N-H of the secondary amide and the urethane carbonyl respectively. An absorption band at 1510 cm^{-1} for the urethane C-N bond gives further proof that the amine group was protected. The carbonyl of the carboxylic acid shows a strong absorption peak at 1745 cm^{-1}.

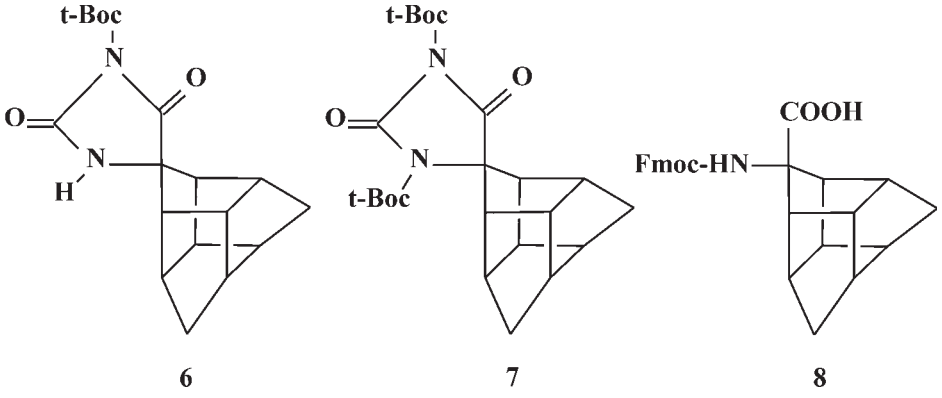

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Figure 3 Protected hydantoins and Fmoc amino acid.

The ^{1}H spectrum of the Fmoc amino acid (**8**) in $(CD_3)_2SO$ exhibits a complex pattern between 1.0 and 3.0 ppm characteristic[5a,12,17,18] of the cage protons. Peaks between 7.2 and 8.2 ppm represent the aromatic protons of the Fmoc group. A low field peak appears at 12.1 ppm due to the carboxylic acid. The ^{13}C NMR shows two carbonyl carbon signals at 174.0 ppm for the acid and 155.4 ppm for the carbamate. Two-methylene carbon resonances are registered at 31.8 ppm and 32.7 ppm for the cage and one signal at 68.7 ppm for the CH_2 of the Fmoc group. The Fmoc group is base-labile and a ninhydrin test indicated that some deprotection of a dry sample had occurred after three weeks of storage in a refrigerator.

As indicated in the introduction, synthesizing trishomocubane amino acid derivatives (such as **8** and **9**) suitable for peptide synthesis, is a worthwhile goal. However, special precaution will have to be taken to overcome the substantial steric factors expected for the α,α-dialkyl substituted trishomocubane amino acid derivatives. The smallest α,α-dialkyl substituted amino acid, amino-isobuteric acid [Aib, $(CH_3)_2C(NH_2)COOH$], is considered to be problematic in solid phase peptide synthesis (SPPS) due to these steric factors[19,20] and therefore activation of the acid function is required.

One popular method used to activate the carbonyl group is by converting it to acid halides. Acid fluorides[21–23] have proven to be more stable than their chloride equivalents,[24–26] often storable for up to six months under normal conditions. They are effective in the coupling of α,α-dialkyl substituted amino acids and highly sterically hindered units such as alamethicin acid [eight Aib and two proline residues].[19]

Synthesis of the Fmoc amino acid fluoride (**9**) seemed therefore to be the most suitable option for potential SPPS applications. The Fmoc amino acid (**8**), upon treatment with cyanuric fluoride,[21,27] yielded the acid fluoride (**9**) in 87% yield (see Scheme 2).

The NMR data of the Fmoc acid fluoride (**9**) corresponds well with the data of the Fmoc acid (**8**) with the expected disappearance of the acid proton at 12.2 ppm and the appearance of the ^{19}F signal at 234.1 ppm. Note that C_4 and $C_{2'}$ show coupling with ^{19}F and are registered as doublets. The high-resolution mass spectrum of **9** exhibits a $[M+H]^+$ peak at m/z 429.1742 which corresponds with the theoretical mass of **9**.

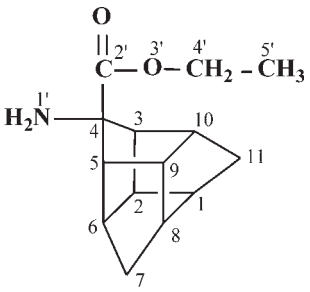

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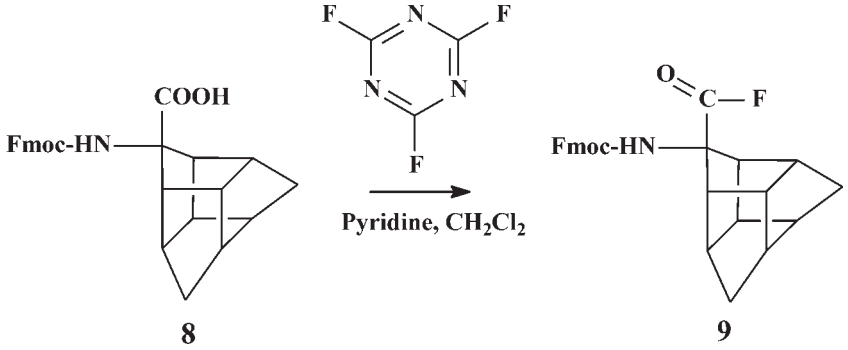
Figure 4 Ethyl ester **10**.

Esterification[28] of the pentacyclo-undecane amino acid (**1**) has proven to be very difficult and has not yet been reported.[3,29] The amino acid (**5**) was, however, successfully esterified as the ethyl ester (**10**) in 70% yield indicating that the acid function of **5** is possibly more suitable than **1** for applications in peptide synthesis.

It was evident that the ethyl ester (**10**) had been synthesized from the $[M+H^+]$ peak of m/z 234 in the mass spectrum, the presence of the carbonyl peak ($C_{2'}$) at 175.74 ppm in the ^{13}C NMR spectrum, and the D_2O exchangeable proton at 1.80 ppm in the ^{1}H NMR spectrum arising from the amino group ($H_{1'}$). The absence of the acid protons at 12.1 ppm is also evident of effective protection of the acid function, which is supported by the loss of the broad acid peak in the IR spectrum at 3380–2850 cm^{-1}.

The multiplet at 4.12–4.18 ppm in the ^{1}H NMR spectrum, which could be assigned to the downfield-shifted methylene



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Scheme 2 Synthesis of the trishomocubane amino acid fluoride **9**.

group ($H_{4'}$) of the ester and the assignment was confirmed by COSY correlations with the $H_{5'}$ methyl protons at 2.07–2.10 ppm. The rest of the carbon and hydrogen signals were assigned using the same methodology used for the elucidation of the hydantoin precursors.[12] The details of the NMR assignments are included in the experimental section.

4. Conclusion

In comparison with conventional hydrolysis of hydantoins, hydrolysis of the bis-Boc-protected hydantoin proved to be a milder method with quantitative yields, despite the additional step. The novel trishomocubane amino acid was also successfully converted to the Fmoc-protected amino acid as well as an amino acid fluoride, which is a more reactive species required for Solid Phase Peptide Synthesis (SPPS). Esterification of the amino acid (**5**) was also achieved for the first time, indicating sufficient reactivity of the acid function required for SPPS.

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