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ORIGINAL ARTICLE

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A silicon-labelled amino acid suitable for late-stage fluorination and unexpected oxidative cleavage reactions in the preparation of a key intermediate in the Strecker synthesis

Kymberley R. Scroggie[1] | Lisa J. Alcock[1] | Maria J. Matos[2] | Gonçalo J. L. Bernardes[2,3] | Michael V. Perkins[1] | Justin M. Chalker[1]

[1]Flinders University, College of Science and Engineering, South Australia 5042, Australia

[2]Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom

[3]Faculdade de Medicina, Universidade de Lisboa, Avenida Professor Egas Moniz, Instituto de Medicina Molecular, Lisboa 1649-028, Portugal

Correspondence
Justin M. Chalker, Flinders University, College of Science and Engineering, South Australia 5042, Australia.
Email: justin.chalker@flinders.edu.au

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Abstract

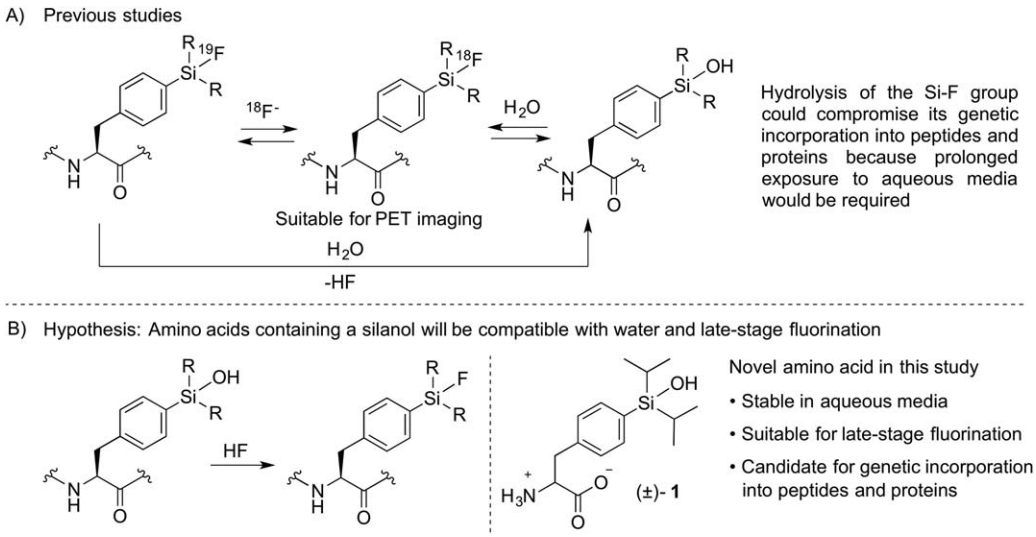
A novel silicon-substituted phenylalanine derivative was prepared using the Strecker amino acid synthesis. An unexpected oxidative cleavage was observed in the preparation of the aldehyde required for the Strecker reaction. In this step, a homobenzylic alcohol intermediate was oxidatively cleaved to the corresponding benzaldehyde using either chromium or palladium based oxidants. This undesired side reaction was overcome through the use of Dess-Martin Periodinane, or through an efficient TEMPO-bleach oxidation. The amino acid prepared in this study was then labelled with fluoride in aqueous solvent using a range of fluoride sources. The efficiency of this labelling motivates future studies in late-stage fluorination of peptide and protein therapeutics for use in positron emission tomography.

KEYWORDS

amino acids, fluorination, oxidative cleavage, PET, silicon, Strecker synthesis

1 | INTRODUCTION

Amino acids that can be labelled with [^{18}F]-fluoride are important for accessing peptides and proteins used in positron emission tomography (PET).[1–9] Silicon-containing amino acids have emerged as useful residues in this context.[10] Among the more common strategies for ^{18}F labelling at silicon is the isotopic exchange of Si-^{19}F for Si-^{18}F (Scheme 1A).[2,10–13] This strategy benefits from good to excellent radiochemical yields and rapid reactions—a necessity given the short half-life of ^{18}F (110 min).[2,12,13] While this strategy has enabled a number of impressive in vivo and pre-clinical studies,[2] the fluorination is typically performed on prosthetic groups (rather than directly on macromolecules) and the Si-F bond is susceptible to hydrolysis.[14] For hindered Si-F groups (e.g., $R = i$-Pr or t-Bu in Scheme 1), this hydrolysis is slow and does not compromise PET applications carried out on time scales shorter than the half-life of hydrolysis.[14] If, however, the amino acid were incorporated into a macromolecule through a biosynthetic route such as amber codon suppression or genetic code reassignment techniques,[15–17] then the hydrolysis may become significant due to the prolonged exposure to aqueous media required during the synthesis and purification. Therefore, we thought it would be useful to consider other silicon-based groups that are stable in water and react efficiently with common fluoride sources. Accordingly, we examined the synthesis and fluorination of silanol-substituted phenylalanine derivative **1** (Scheme 1B). In the preparation of this novel amino acid, we discovered some unexpected reactions in the oxidation of a homobenzylic alcohol intermediate. We also established that **1** is stable in buffer and can be labelled directly with fluoride in aqueous media.



SCHEME 1 Silicon-containing amino acid residues are useful in the direct fluorination of peptides and proteins for PET imaging. A, Isotopic exchange is a common strategy for installing $^{[18]}$F into peptides and proteins. The Si-F group may hydrolyse slowly in water. B, An amino acid labelled with a silanol is proposed in this study as an alternative group that can be labelled directly with a fluoride source such as HF. The proposed target **1** was expected to be stable to aqueous media, which may be useful if it is incorporated into peptides and proteins using a biosynthetic pathway

2 | MATERIALS AND METHODS

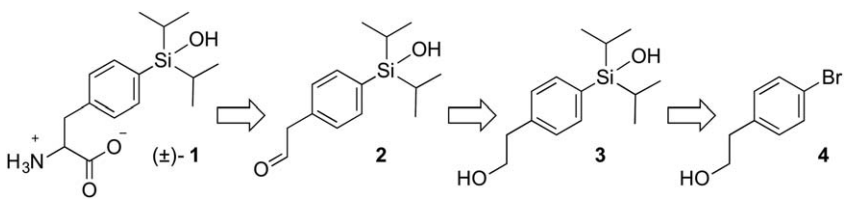
Detailed protocols for all experiments, $^{[1]}$H and $^{[13]}$C NMR spectra, and additional analytical characterization are provided in the Supporting Information.

3 | RESULTS AND DISCUSSION

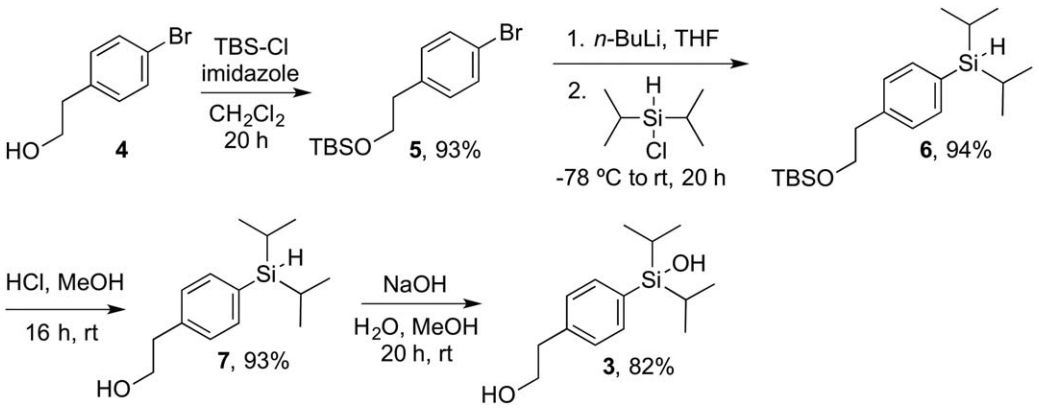
We planned to synthesize the novel amino acid (±)-**1** using the Strecker reaction[18–20]—a strategy used previously for related amino acids.[10] This route would require key aldehyde intermediate **2**, which in turn could be obtained from the oxidation of the corresponding homobenzylic alcohol **3**. To install the silicon group intended as the site for fluorination, a lithiation-silylation was envisioned, with the synthesis beginning with arylbromide **4** (Scheme 2). In the long-term, we plan to use **1** as a building block for peptides and proteins using biosynthetic pathways. For this reason, the racemic amino acid was viewed as an appropriate target because of the biosynthetic selectivity generally observed for the incorporation of L-phenylalanine and its derivatives over their enantiomers during ribosomal biosynthesis of peptides and proteins.[21,22]

In the synthesis, alcohol **4** was first protected by reaction with TBS-Cl to provide silyl ether **5** in 93% yield. Next the silicon group was installed through lithium halogen exchange of **5** with *n*-BuLi, and subsequent reaction of the resulting aryllithium with diisopropylchlorosilane which provided **6** in 94% yield. TBS removal under acidic conditions gave alcohol **7** in 93% yield. Subsequent oxidation of the silane to the silanol in a basic solution of water and methanol provided the key homobenzylic alcohol intermediate **3** in 82% yield (Scheme 3). More than 4.0 g of **3** was prepared by this route.

Up to this stage the synthesis had proceeded smoothly, but the conversion of homobenzylic alcohol **3** to the aldehyde intermediate **2** proved to be an unexpected challenge. The use of pyridinium chlorochromate (PCC) resulted in the oxidative cleavage of the C—C bond joining the benzylic and homobenzylic carbon atoms, providing benzaldehyde **8** as an undesired product (Scheme 4, Entries 1–4). While there is precedence for chromium-based oxidative cleavage reactions of homobenzylic alcohols,[23–26] we were still surprised by the high conversions observed for this unwanted reaction. For instance, up to 90% conversion to the undesired benzaldehyde **8** was observed with excess PCC (4 equivalents) within 6 hr of reaction time at room temperature (Scheme 4, Entry 1). This result was curious given a previous report in which a similar aldehyde was prepared using chromium based oxidations under similar conditions without mention of this side reaction.[10] Using two equivalents of PCC still resulted in a mixture of **2** and **8**, and using only one equivalent resulted in a mixture of aldehydes **2** and **8**,



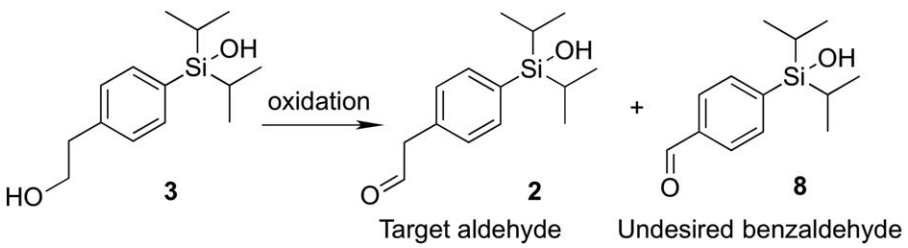
SCHEME 2 Retrosynthetic analysis of (±)-**1**



SCHEME 3 The synthesis of alcohol intermediate **3**

as well as unreacted alcohol **3** (Scheme 4, Entries 3–4). While the mechanistic details for the oxidative conversion of homobenzylic alcohols to benzaldehydes have not been studied,[23–26] we suspect that the homobenzaldehyde is an intermediate in the process. For instance, treating purified **2** with 1 equivalent of PCC resulted in the formation of **8** (see page S23 in the Supporting Information). This result confirms the hypothesis that homobenzaldehyde **2** can be an intermediate in the conversion to **8** and that this oxidative cleavage also applies to homobenzaldehydes. Pyridinium dichromate (PDC) also led to the unwanted oxidative cleavage, providing the undesired benzaldehyde **8** in 85% conversion after 3 hr of reaction at room temperature when 4 equivalents of the oxidant were used (Scheme 4, Entry 5).

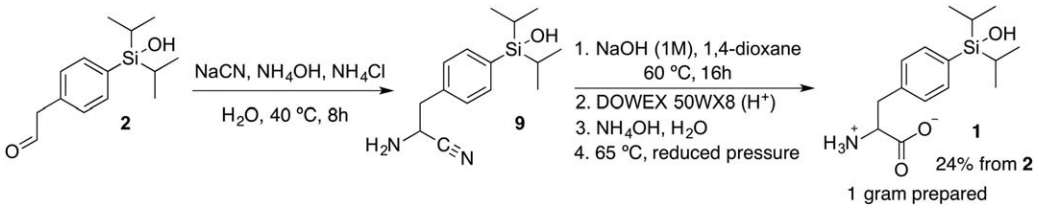
Interestingly, this oxidative cleavage was also observed when using Uemura's palladium catalysed aerobic oxidation,[27] with a 2:1 ratio of **2**:**8** observed by ^{1}H NMR (Scheme 4, Entry 6). While unreacted starting material was still the major product in this reaction (64% unreacted **3** was indicated by ^{1}H NMR), the oxidative cleavage is still notable because it was not reported in other studies on the palladium catalysed



Entry	Oxidant	Amount	Reaction Time (hours)	Product distribution 3	2	8
1	PCC	4 equiv.	6	0%	9%	91%
2	PCC	4 equiv.	3	0%	36%	64%
3	PCC	2 equiv.	3	0%	73%	27%
4	PCC	1 equiv.	3	66%	19%	15%
5	PDC	4 equiv.	3	0%	15%	85%
6	$Pd(OAc)_2$ O_2	5 mol% 1 atm	2	64%	24%	12%
7	DMP	1.5 equiv.	18	46%	54%	0%
8	DMP	4 equiv.	18	0%	70%*	0%
9	DMP	4 equiv.	1.5	0%	60%*	0%
10	**TEMPO NaOCl**	**5 mol% 1.1 equiv.**	**0.5**	**0%**	**70%***	**0%**

* isolated yields

SCHEME 4 When using either chromium or palladium-based oxidants, alcohol **3** was converted to a mixture of the desired aldehyde **2** and the undesired benzaldehyde **8**. Using either Dess-Martin Periodinane (DMP) or TEMPO/NaOCl as oxidants prevented the undesired oxidative cleavage reaction and both methods provided **2** in good yields. Product distributions were determined directly by ^{1}H NMR spectroscopy for Entries 1–7 and isolated yields are reported for Entries 8–10



SCHEME 5 The Strecker reaction provided the target amino acid (±)-**1**

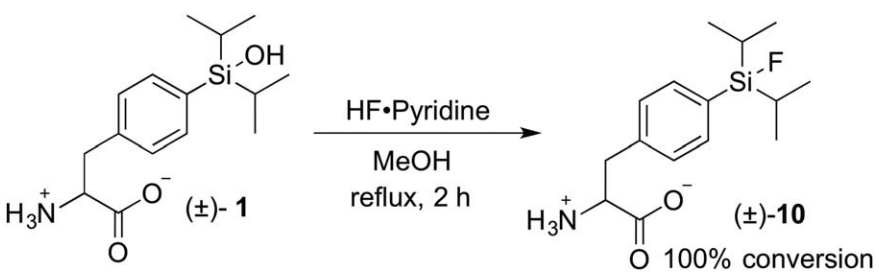
aerobic oxidation of homobenzylic alcohols,[28–33] so this transformation may be dependent on the specific catalyst system. In any case, this is the only example of which we are aware where Uemura's aerobic oxidation leads to oxidative cleavage of a carbon–carbon bond for homobenzylic alcohols. We also note that similar oxidative cleavage was observed with the substrate 2-phenylethanol when using either Uemura's oxidation or PCC, so the silicon group is not required for this transformation (see pages S24–S25).

It is important to note that even small amounts of **8** are inconvenient because it was challenging to separate **2** and **8** by column chromatography. Therefore, we turned to other oxidations to overcome the unwanted C—C cleavage. Dess-Martin Periodinane (DMP)[34] did not provoke the oxidative cleavage, though the reaction was sluggish with only 54% of the desired aldehyde **2** formed after 18 hr with 1.5 equivalents of DMP. When using four equivalents of DMP, full conversion was observed after 18 hr and **2** was isolated in a 70% yield. Shorter reaction times with four equivalents of DMP resulted in slightly lower yields, with **2** isolated in 60% yield after 1.5 hr (Scheme 4, Entry 9). This protocol was important in providing pure **2**, but we considered that the excess DMP required and the low atom economy of the oxidation were not ideal for up-scaling. Therefore, the key oxidation was also tested using TEMPO and sodium hypochlorite.[35] Gratifyingly, this oxidation was highly efficient and provided aldehyde **2** in 70% yield after only 25 min of reaction time at <10°C (Scheme 4, Entry 10). The temperature of the reaction mixture was controlled to avoid decomposition of oxoammonium intermediate derived from TEMPO,[35] and the reaction progression was monitored carefully so that it could be quenched before overoxidation to the corresponding acid. Even with these precautionary measures, we note that this oxidation is operationally simple, rapid and high yielding. This outcome should encourage future use of the TEMPO and sodium hypochlorite oxidants in the synthesis of homobenzylic aldehydes, including those advanced to various phenylalanine derivatives through the Strecker reaction.

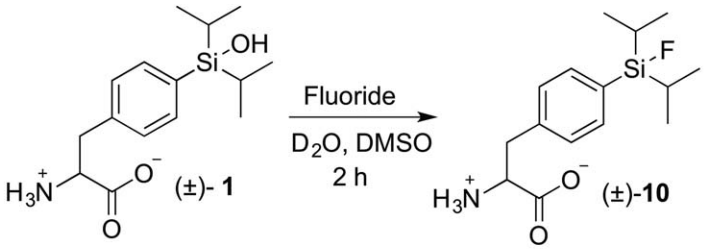
The synthesis of (±)-**1** was completed using the Strecker reaction in which aldehyde **2** was first reacted with sodium cyanide, ammonium hydroxide and ammonium chloride to form amino nitrile **9**, which was used directly without purification. Hydrolysis of the crude amino nitrile **9** under basic conditions, followed by purification by ion exchange chromatography provided the target compound as a crystalline solid (Scheme 5).

While the yield of **1** after the Strecker sequence and ion exchange chromatography was relatively low (24% in the conversion of **2** to **1**), more than 1.0 g of **1** was prepared. With this quantity in hand, we could study the reaction of **1** with various fluoride sources. To obtain a benchmark, HF•Pyridine was tested first in its reaction with **1** in refluxing methanol. Gratifyingly, after 2 hr, full conversion to **10** was observed (Scheme 6). This result was encouraging in that the fluorination occurred readily even in a protic solvent that could hydrogen bond to fluoride and potentially attenuate its reactivity.

Next, the fluorination was tested with a variety of fluoride sources using aqueous DMSO or buffers as solvent (Scheme 7). HF•Pyridine was tested first using a 3:1 ratio of DMSO:D_2O by volume and the reaction temperature was set to 95°C. Full conversion of **1** to **10** was observed within 2 hr, as indicated by both $^{[1]}H$ and $^{[19]}F$ NMR spectroscopy (Scheme 7, Entry 1). The formation of the Si—F bond was consistent with a signal at −182.15 ppm in the $^{[19]}F$ NMR spectrum. The $^{[1]}H$ NMR spectrum of **1** and **10** were also easily resolved with significant differences in chemical shift for the signals corresponding to the aromatic and isopropyl protons. This distinction allowed calculation of reaction conversions where mixtures of **1** and **10** were formed (Scheme 7). Pleasingly, full conversion was also observed at 37°C under otherwise identical conditions (Scheme 7, Entry 2). Successful fluorination at the lower temperature is important if this reaction is to be adapted to proteins. Perhaps just as important, the fluorination of **1** was also possible using a solution of HF in water, with only 10% volume of DMSO in the reaction mixture. For fragile proteins that are incompatible with high levels of organic solvents, this is an important



SCHEME 6 The fluorination of **1** in methanol



Entry	Fluoride Source (10 eq.)	Temperature	Buffer pH	DMSO (% vol.)	Conversion (^{1}H NMR)
1	HF•Pyridine	95 °C	-	75%	100%
2	HF•Pyridine	37 °C	-	75%	100%
3	HF in H_2O	37 °C	-	10%	100%
4	HF in H_2O	37 °C	4	10%	60%
5	HF in H_2O	37 °C	8	10%	58%
6	KF	95 °C	4	0%	38%

SCHEME 7 Fluorination of amino acid (±)-**1** in aqueous solvents

capability. When the reaction was buffered (either at pH 4 or pH 8), slightly lower conversions of 60 and 58% were observed in the respective fluorination (Scheme 7, Entries 4–5), but this is still substantial labelling in the context of PET. It should also be noted that in buffered media, the addition of 10% DMSO as a co-solvent helped keep **1** in solution. However, over the course of these buffered reactions the amino acid precipitated, which could account in part for the lower conversions. Finally, KF was examined as a fluoride source. At pH 4, 38% conversion was observed after 2 hr at 95°C (Scheme 7, Entry 6). Notably, no DMSO was used in this experiment. While this conversion was lower than the other reactions examined in Schemes 6 and 7, it was notable that KF could be used directly, without the need for the crypt- and Kryptofix$_{222}$, which is commonly used to bind to potassium ions and make the fluoride more nucleophilic.[36] Additionally, the successful fluorination using HF or KF is important because both can be formed directly from the [^{18}F]-fluoride produced for PET imaging.[36]

The direct labelling of an amino acid with fluoride in aqueous media, as demonstrated in Scheme 7, is noteworthy because it is far more common to react [^{18}F]-fluoride with a silicon-containing reagent in an organic solvent and then ligate that reagent to a peptide or protein in a second step.[2,37–42] There are far fewer examples of labelling proteins with [^{18}F]-fluoride directly at a well-defined site, in aqueous buffer, and in the final step. In these rare cases, the fluoride reactive group is typically ligated to the protein as a prosthetic group before fluorination.[43] In contrast, genetically encoded incorporation of **1** would provide the fluoride reactive group directly on the protein during biosynthesis. Labelling such a peptide or protein with [^{18}F]-fluoride in the final step may also be useful in obtaining higher radiochemical yields because only one reaction and purification would be required, as opposed to multi-step reactions that require precious time over which the radioisotope decays. The results in Schemes 6 and 7 suggest that **1** is worth exploring in this context. Accordingly, we are currently investigating methods to biosynthetically incorporate amino acid **1** into peptides and proteins, for direct labelling with [^{18}F]-fluoride in the final step. We anticipate such capabilities will find ultimate use in the synthesis of peptides and proteins that can be imaged by PET.

4 | CONCLUSIONS

The gram-scale synthesis of a novel amino acid (±)-**1** was accomplished. This amino acid contains a silanol group that can be labelled with multiple fluoride sources with useful conversions—even when water is the primary solvent. This capability motivates future exploration in the genetic incorporation of **1** into peptides and proteins for subsequent [^{18}F]-labelling and use as tracers in PET imaging. In the synthesis of (±)-**1**, an undesired oxidative cleavage of a homobenzylic alcohol was discovered when using either chromium or palladium-based oxidants. This side reaction was so efficient in certain cases (e.g., >90% conversion was observed with four equivalents of PCC) that it might find use as a synthetic method in other contexts. The oxidative cleavage using palladium is notable because this type of transformation has not been reported for this catalyst system. Using either DMP or a TEMPO/NaOCl oxidant overcame this unwanted oxidative cleavage and provided a convenient route to the required aldehyde. These oxidation protocols may be also useful in the synthesis of other phenylalanine derivatives prepared via the Strecker method.

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ORCID

Justin M. Chalker http://orcid.org/0000-0002-7504-5508

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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