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Synthesis of novel sila-substituted β-amino acids

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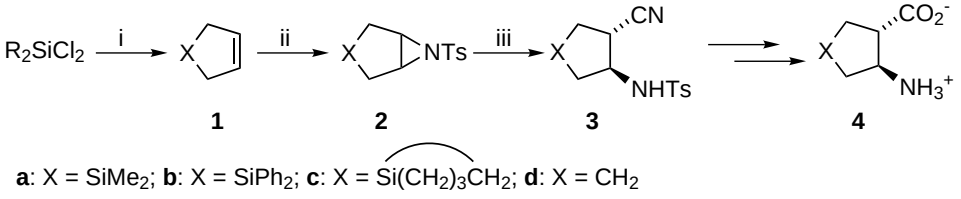
Abstract—A highly efficient and stereoselective synthesis of unnatural cyclic sila-substituted β-amino acids has been developed from simple starting materials. The key step is nucleophilic ring opening of an intermediate aziridine with an *umpolung* synthon for the carboxylate anion. Functional group manipulation and deprotection reactions allow access to the desired *trans* β-amino acids.

1. Introduction

β-Amino acids have received a great deal of attention from synthetic chemists over the last decade and this is in part due to their important applications in medicinal chemistry.[1] For example, cyclic and linear oligomers of β-amino acids have been shown to exhibit high biological activity as mimics[2] for the peptide hormone somatostatin and cyclo-β-tripeptides have been shown to be antiproliferatives against human cancer cell lines.[3]

We wish to extend this range by synthesising a series of novel cyclic sila-substituted β-amino acids. Sila-substitution, the replacement of a carbon atom by a silicon atom in a compound with biological activity, has been shown to generate compounds with differing physicochemical properties, chemical reactivity and biological activity. This phenomenon has been used in the search for improvements in a number of areas of medicinal chemistry.[4] In particular, the use of trimethylsilylalanine as a bioisosteric replacement for phenylalanine has been shown to improve biological stability of certain



Scheme 1. *Reagents and conditions*: (i) Cp_2TiCl_2 (5 mol%), $H_2C{=}CHMgBr$ (2.1 equiv.), THF, –40°C, 4 h; (ii) Chloramine-T (1.1 equiv.), PTAB (10 mol%), MeCN, rt, 5 h; (iii) Et_2AlCN (4 equiv.), PhMe, 100°C, 17 h.

Table 1.

	Step (i) yield (%) of **1**	Step (ii) yield (%) of **2**	Step (iii) yield (%) of **3**
a	79	67	75
b	77	81	73
c	45	65	72
d	n/a	89	70

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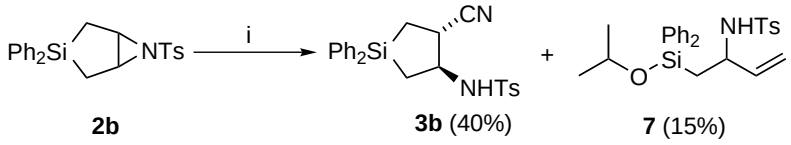


2b **3b** (40%) **7** (15%)

Scheme 2. *Reagents and conditions*: (i) $Me_2C(OH)CN$, $Yb(OiPr)_3$, THF, 50°C.

peptidomimetics whilst retaining biological activity. Herein we describe the synthesis of several novel β-amino acids containing silicon in a five-membered ring.

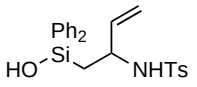
2. Discussion

Synthesis of the unnatural amino acids was achieved by following the route outlined in Scheme 1. This involves aziridination of the silacyclopent-3-ene **1**, affording aziridines **2**. Ring opening methodology gave the cyano compounds **3**, followed by amine deprotection and nitrile hydrolysis yielding the target β-amino acids **4**. We have also used the described methodology to synthesise a carbon-based amino acid **4d**, where the R_2Si moiety is replaced by H_2C. This amino acid will be used as a comparison with our silicon based compounds in biological testing studies.

The silacyclopent-3-ene starting materials **1a**–**c** were obtained using the titanocene dichloride catalysed reaction system of Watabe (Scheme 1).[5] The cyclopentene products were obtained in 45–79% yields (Table 1). This methodology proved to be far superior to alternative strategies[6] with improved yields and a wider range of silacyclopent-3-enes being made available. The use of cyclopentene **1d** as the starting material leads to the formation of the carbon analogue **4d**.

The key intermediates in our syntheses, aziridines **2**, were prepared directly from **1** using the Chloramine-T/PTAB system of Sharpless (Scheme 1, Table 1).[7] X-Ray crystal structure analysis of bicyclohexane **2b** revealed unexpected potential transannular H-bond interactions across the ring system between the nitrogen lone pair and an aromatic C–H group. We have already described[8] some of our work in this area and further crystallographic studies are currently underway to determine the exact nature of this interaction.

The key ring opening step required extensive experimentation, with several Lewis acids and sources of cyanide being screened. Treatment of aziridine **2b** with $KCN/t\text{-}Bu_4NCN$ in THF/water resulted in undesirable ring opening at silicon, by either water or CN^-. Interesting by-products **5** and **6** were identified, and their formation rationalised by comparison with literature precedent: the initial adduct could be formed by nucleophilic attack of cyanide at silicon. The resulting nitrile is thought to be in equilibrium with the less stable isonitrile which may be rapidly hydrolysed in the presence of water to the observed by-product **5**.[9] Silanol **5** slowly dimerises upon standing at room temperature, eliminating water to form the disiloxane **6**.



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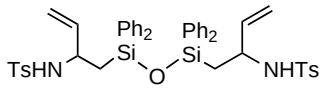

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We then turned our attention to the use of lanthanide based reagents. Inoue's procedure[10] involving the use of acetone cyanohydrin as a source of CN^- with a triva-

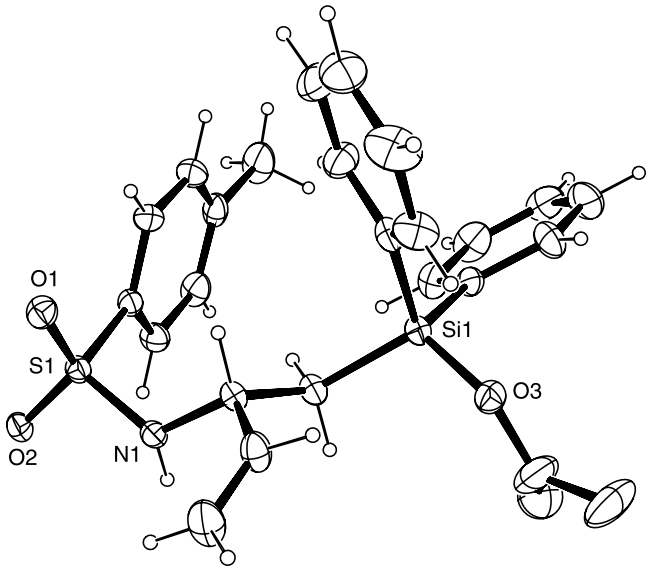

Figure 1. X-Ray crystal structure analysis of **7**. Isopropyl hydrogens are omitted.

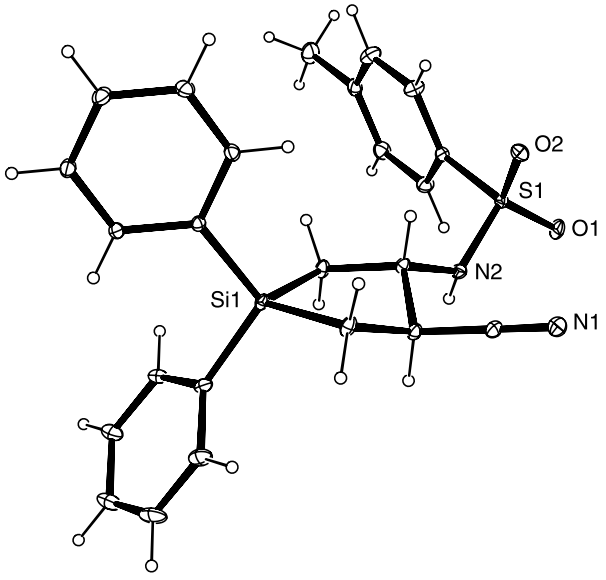

Figure 2. X-Ray crystal structure analysis of **3b**.

lent ytterbium alkoxide (10 mol%) resulted in the formation of **3b** in 40% yield (Scheme 2). A side reaction was also observed during this reaction: ring opening at silicon by isopropoxide is observed resulting in the formation of the unusual alkoxysilyl species **7**. The structure of this surprisingly stable by-product has been confirmed by X-ray crystal structure analysis (Fig. 1). This compound opens up further potential for the development of novel amino acid analogues and we are now investigating its potential.

Eventually, we established that the method of choice for the stereoselective aziridine ring cleavage involves the use of Et_2AlCN (Nagata's reagent)[11] and gives exclusively *anti* attack at the aziridine ring to yield racemic nitrile products **3** in high yield (Scheme 1, Table 1). The stereochemistry of **3b** was proven by X-ray crystal structure analysis (Fig. 2).

Removal of the tosyl group from **3** was achieved in excellent yield by initially protecting the amine with a Boc group under DMAP catalysis, giving adducts **8** (Scheme 3, Table 2). Reduction with magnesium chips in methanol under the conditions developed by Ragnarsson resulted in mild detosylation affording the Boc protected amines **9**.[12,13] Direct hydrolysis of the aminonitriles **9** to the amino acid **4** was problematic. Cleavage of the five-membered silacycle was observed under basic conditions and the nitrile proved unreactive towards aqueous acid.

Nitrile **9** was therefore converted into the ethyl ester **10** using anhydrous ethanol saturated with HCl, then saponified with NaOH to give amino acid **4** (Scheme 3, Table 2). The nitrile **9d** was converted directly into the amino acid **4d** simply by heating in concentrated HCl (aq.). We are currently investigating the resolution of esters **10** under enzymatic hydrolysis conditions, using *Candida antartica* lipase immobilised on a solid support. Enantiomeric excesses of up to 47% have been obtained thus far, and work is ongoing in this area.

3. Conclusion

A highly efficient and stereoselective route to unnatural sila-substituted β-amino acids has been developed, incorporating the key ring opening reaction of aziridines **2** with a commercially available source of CN^-.† We are currently investigating incorporation of our amino acids into β-peptides and analogues of known drugs to compare their biological activities with those of the corresponding carbon analogues.

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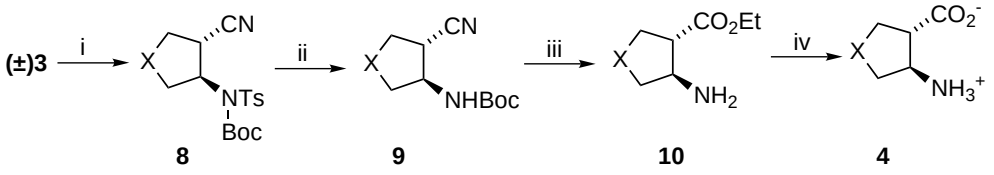

Scheme 3. *Reagents and conditions*: (i) Boc_2O (1.3 equiv.), DMAP (10 mol%), MeCN, rt, 5 h; (ii) Mg (10 equiv.), MeOH, sonication, 40 min; (iii) saturated HCl in EtOH, rt, 22 h; (iv) 2 M NaOH (aq.) rt, 22 h.

Table 2.

	Step (i) yield (%) of **8**	Step (ii) yield (%) of **9**	Step (iii) yield (%) of **10**	Step (iv) yield (%) of **4**
a	95	98	95	78
b	98	81	97	88
c	99	97	90	86
d	98	92	n/a	85

† Typical experimental procedure for ring opening: diethylaluminium cyanide (24.8 mL, 0.0248 mol, 1 M in toluene) was added dropwise to a stirred solution of 4-aza-4-tosyl-1,1-diphenyl-1-silabicyclo[3.1.0]hexane (2.512 g, 6.196 mmol) in toluene (12 mL). The reaction mixture was then heated at 100°C for 17 h, after which time the reaction was quenched by pouring it portionwise onto a mixture of fresh ice and NaOH (150 mL, 2 M aq. solution). The aqueous layer was extracted with DCM (3×100 mL). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated in vacuo to yield the crude product. Flash chromatography eluting with petroleum ether–EtOAc (3:1) yielded the desired product as a white solid. Recrystallisation from petroleum ether–EtOAc yielded white needles (1.957 g, 73% yield).

‡ Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 184658 and 184659. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].

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