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SHORT COMMUNICATION

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Synthesis of Optically Active Selenium-Containing Isotryptophan, Homoisotryptophan, and Homotryptophan

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Selenoisotryptophan and its higher homologues were synthesized by Sonogashira coupling of iodophenyl methyl selenide and alkynyloxazolidines followed by iodocyclization as the key step. Sonogashira coupling of 3-iodobenzoselenophene with ethynyloxazolidine allowed the synthesis of selenohomotryptophan.

Introduction

Selenium-containing unnatural amino acids are well known to reduce phase problems in protein crystallography.[1a,1b] In the last decade, selenium analogues of tryptophan (i.e., **1a** and **1b**; Figure 1) are found to be used in this direction.[1c] Besides crystallography, amino acids bearing radioactive selenium are used for imaging purpose. In this area, different selenium-substituted aromatic or heterocyclic α-amino acids (e.g., **1d**, **1e**)[2a] have been synthesized as model compounds. Radioactive Se^{75} labeled tryptophan **1c** is in clinical trials as a pancreatic scanning agent.[2b]

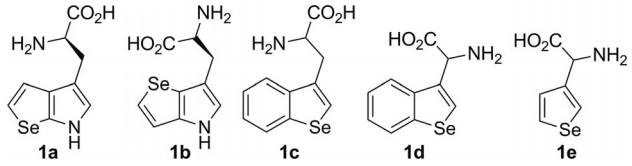
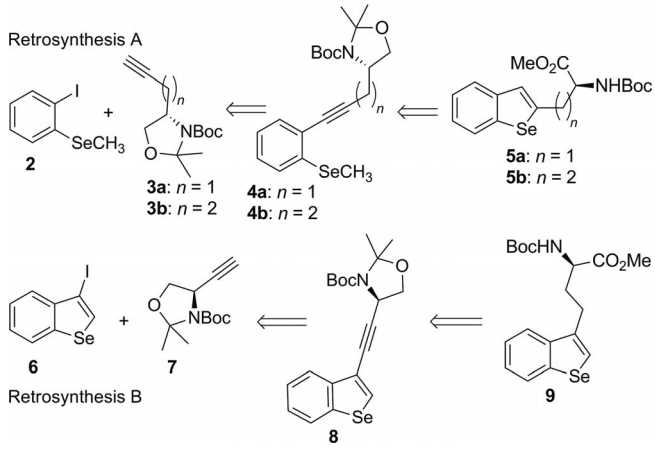


Figure 1. Important selenotryptophan analogues.

As part of our ongoing research toward the synthesis of tryptophan analogues, we decided to prepare new Se analogues in optically active form. Herein we report the synthesis of selenium-containing isotryptophan **5a**, homoisotryptophan **5b** and homotryptophan **9** by using a chiral pool approach.

Results and Discussion

Our retrosynthetic route is depicted in Scheme 1; suitably substituted alkynyloxazolidines were used as building blocks for the introduction of a chiral center to the amino acids. We anticipated that selenoisotryptophan **5a** and its higher homologue **5b** could possibly be synthesized by iodocyclization[3] of intermediate **4**, which could be obtained by Sonogashira coupling[4] of iodophenyl methyl selenide (**2**)[3a,3b] with alkynyloxazolidines **3a** and **3b**[5a–5d] (retrosynthesis A, Scheme 1). The synthesis of selenohomotryptophan **9** could be achieved from intermediate **8**, which in turn could be synthesized by Sonogashira coupling of 3-iodobenzoselenophene (**6**)[3a] and ethynyloxazolidine **7**[6] (retrosynthesis B, Scheme 1).



Scheme 1. Retrosynthetic pathway.

The synthesis of tryptophan analogues was previously reported by Rutjes et al.[7] by using Sonogashira coupling as the key step; however, a similar synthesis of the Se analogues has not been attempted. Moreover, the starting acetylene-containing α-amino acids were prepared by a chemoenzymatic method, as these compounds are very expensive commercially. Recently, we developed a strategy to prepare indole/benzofuran-containing amino acids through the palladium-catalyzed coupling of alkynyloxazolid-

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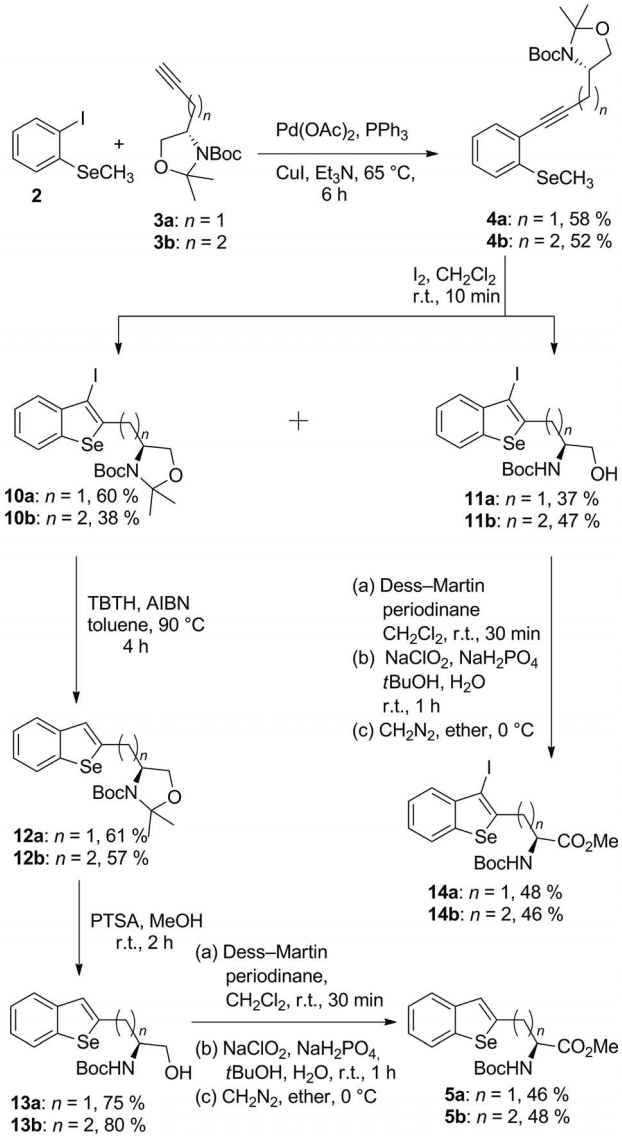
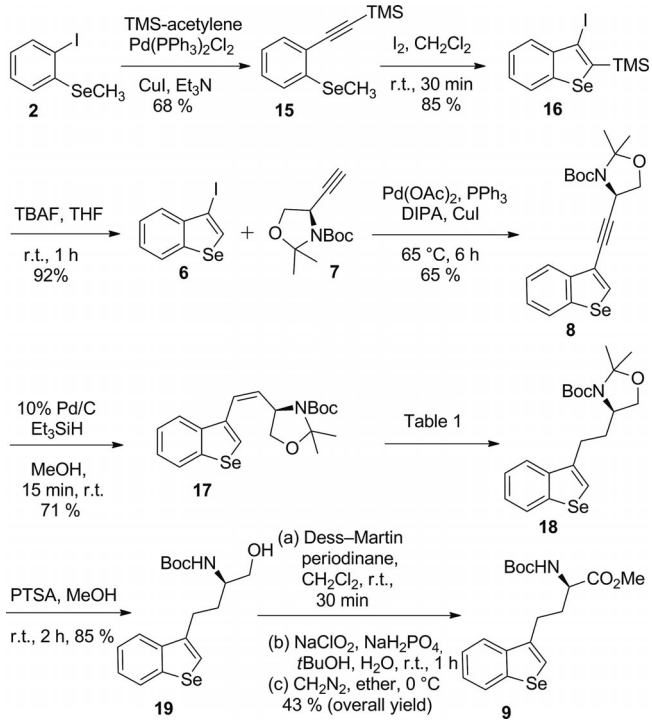
ines.[5d,5e] At the onset of the synthesis, we prepared iodophenyl methyl selenide **2**[3a,3b] from commercially available 2-iodoaniline. This was then coupled with acetylene **3a** to form adduct **4a**. Upon treatment with iodine in dichloromethane at room temperature, compound **4a** gave desired **10a** in 60% yield along with amino alcohol **11a** as a result of the Lewis acidic behavior of molecular iodine. Deiodination[8] of **10a** by using tributyltin hydride (TBTH) in the presence of 2,2′-azobisisobutyronitrile (AIBN) afforded **12a**, which after acetonide removal under acidic conditions provided deiodinated amino alcohol **13a**. Sequential oxidation[9] and esterification afforded selenoisotryptophan **5a** from **13a**. Repetition of the same sequence with **11a** led to the formation of 3-iodoselenoisotryptophan derivative **14a**. Similarly, higher homologue **5b** and iodo derivative **14b** were prepared from butynyloxazolidine **3b** and selenide **2** by following the reaction sequence shown in Scheme 2. Chiral acetylenes **3a** and **3b** were synthesized from naturally occurring L-aspartic acid and L-glutamic acid according to a literature procedure.[5a–5d]



Scheme 2. Synthesis of selenoisotryptophan and selenohomoisotryptophan derivatives (PTSA = *p*-toluenesulfonic acid).

Synthesis of selenohomotryptophan **9** commenced with the preparation of 3-iodobenzoselenophene (**6**)[3a] from iodophenyl methyl selenide (**2**). Compound **6** was then coupled with ethynyloxazolidine **7**[6] under Sonogashira[4] conditions to obtain coupling product **8**. Ethynyloxazolidine **7** was made from Garner's aldehyde,[6] which in turn was prepared from naturally occurring L-serine. Application of standard hydrogenation[10] conditions to reduce the triple bond of **8** resulted in a mixture of half-saturated product **17**, completely saturated product **18**, and starting material **8**, in which **17** was the major species (Scheme 3). Hydrogenation at high (>80 psi) pressure[10] provided a parallel outcome (Scheme 3).

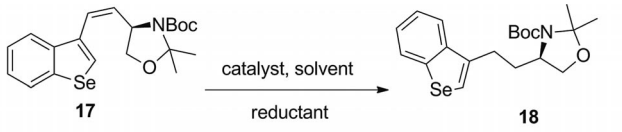


Scheme 3. Synthesis of selenohomotryptophan derivative from iodophenyl methyl selenide (TBAF = tetrabutylammonium fluoride, DIPA = diisopropylamine, PTSA = *p*-toluenesulfonic acid).

After purification, semisaturated compound **17** was subjected to hydrogenation under several conditions[10] (Table 1, entries 1–6) but none of these provided **18** in more than 7% yield.

However, overnight hydrogenation in a Parr hydrogenator (>80 psi) afforded desired product **18** in moderate yield (Table 1, entry 7). Unreacted starting material **17** was recovered in every case (Scheme 3). At this juncture, acetonide deprotection of **18** resulted in amino alcohol **19**, which upon oxidation[9] and esterification afforded selenohomotryptophan derivative **9** (Scheme 3).

Table 1. Conditions for the reduction of the double bond to a single bond.[a]



Entry	Catalyst	Amount	Reductant	Time [h]	Yield[b] [%]
1	10 % Pd/C	15 wt.-%	Et_3SiH[c]	2	5
2	10 % Pd/C	15 wt.-%	H_2 (1 atm)	12	7
3	$NiCl_2$	50 mol-%	$NaBH_4$[d]	4	–[e]
4	$Pd(OH)_2$	10 wt.-%	H_2 (1 atm)	12	6
5	$RhCl(PPh_3)_3$	10 mol-%	H_2 (1 atm)	12	6
6	PtO_2	10 mol-%	H_2 (1 atm)	5	–[e]
7	10 % Pd/C	20 wt-%	H_2 (>80 psi)	24	40

[a] Reagents and conditions: Reactions were performed with **17** (0.05 mmol) in methanol (1 mL, entries 1 to 5) and AcOH (1 mL, entry 6). Reaction was performed with **17** (0.26 mmol) in methanol (20 mL, entry 7). 1 psi = 6.89 kPa; 1 atm = 101.32 kPa. [b] Isolated yield. [c] Et_3SiH (10 equiv.). [d] $NaBH_4$ (1.5 equiv.). [e] No reaction.

Conclusions

In summary, the synthesis of optically active new selenotryptophan analogues was reported from alkynyloxazolidines by using a chiral pool approach. Though the yield in the reduction step was moderate, the synthesis of selenohomotryptophan is reported for the first time. During their synthesis, we prepared 3-iodosusbtituted analogues that can be further derivatized by standard coupling reactions to afford several other analogues.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data, ^1H NMR spectra of all new compounds and ^{13}C NMR spectra of compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **8**, **9**, **12a**, **12b**, **13a**, **13b**, **14a**, **14b**, **17**, **18**, and **19**.

Acknowledgments

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