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Letter

Toward Enantiomerically Pure β-Seleno-α-amino Acids via Stereoselective *Se*-Michael Additions to Chiral Dehydroalanines

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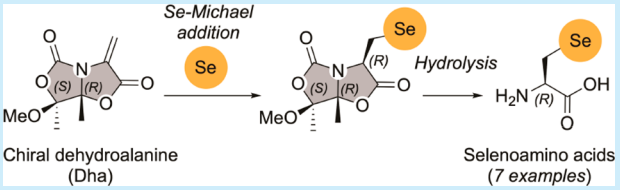
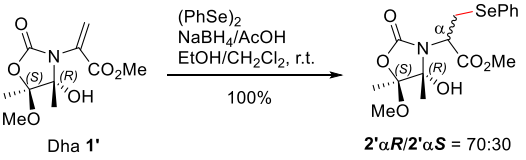
ABSTRACT: The first totally chemo- and diastereoselective 1,4-conjugate additions of *Se*-nucleophiles to a chiral bicyclic dehydroalanine (Dha) are described. The methodology is simple and does not require any catalyst, providing exceptional yields at room temperature, and involves the treatment of the corresponding diselenide compound with $NaBH_4$ in the presence of the Dha. These *Se*-Michael additions provide an excellent channel for the synthesis of enantiomerically pure selenocysteine (Sec) derivatives, which pose high potential for chemical biology applications.



Selenocysteine (Sec, U) is the 21st genetically encoded amino acid, which is inserted cotranslationally into many proteins, providing different selenoproteins with a variety of appreciated redox properties.[1,2] Different post-translational modifications of Sec in selenoproteins have been experimentally validated,[2b] and selenoamino acids have been used in site-selective protein modification (SSPM) as precursors of dehydroalanine (Dha) enabling the introduction of post-translational modifications or chemical tags in proteins.[2] Beyond applications in bioconjugation, selenoamino acids are particularly relevant in native chemical ligation (NCL), a versatile chemical approach to prepare large peptides and proteins that has revolutionized the field of protein science.[3] The fundamental improvement of ligation chemistry using selenoamino acids is that chemoselective deselenization can be accomplished under mild conditions.[4] Moreover, the Sec-driven NCL is faster, more pH tolerant, and efficient than Cys-driven NCL,[5] allowing the synthesis of selenoproteins in high yields.[6] In addition, some *Se*-protected Sec, which can be deprotected and activated on demand, have been genetically incorporated into proteins.[7a,b] Several aryl derivatives of Sec serve as chemical models to understand the inhibition of selenoenzymes, which has implications for cancer therapy.[7c] Thus, synthetic methodologies for generating libraries of diverse enantiomerically pure selenoamino acids are valuable to facilitate access to selenopeptides and selenoproteins.[7]

Selenoamino acids in enantiomerically pure forms are commonly obtained by nucleophilic substitution reactions. In this regard, various methods to generate selenated nucleophiles have been described, especially focusing on the ring-opening reactions of heterocycles to access a variety of organo-selenium compounds, including their chiral variants.[8,9] Although the *Se*-nucleophilic substitution reaction has been deeply explored, less attention has been paid to 1,4-conjugate addition reactions. A few examples reported that treatment of α,β-unsaturated carbonyl derivatives with nucleophilic selenium species affords β-seleno derivatives through Michael-like addition reactions.[10] However, to the best of our knowledge the asymmetric 1,4-conjugated addition of *Se*-nucleophiles to chiral Michael acceptors has not been reported. Hence, and following the methodology established by our group,[11] we envisioned the synthesis of enantiopure selenoamino acids using the *Se*-nucleophilic 1,4-attack to chiral dehydroalanines as a key step. First, we assayed the 1,4-conjugated addition using our first generation chiral Dha **1′** as a Michael acceptor (Scheme 1).[11a,b]

Scheme 1. Stereoselective *Se*-Michael Addition to Dha 1′



Dha **1′** — **2′αR/2′αS** = 70:30

Phenylselenolate generated *in situ* from diphenyl diselenide **a** in the presence of $NaBH_4$ and acetic acid was used as a nucleophile in ethanol/dichloromethane (9:1) at room temperature (Scheme 1). The reaction was fast and quantitative, although a 70:30 mixture of two diastereoisomers was detected by ^1H NMR (Supporting Information).

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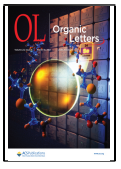

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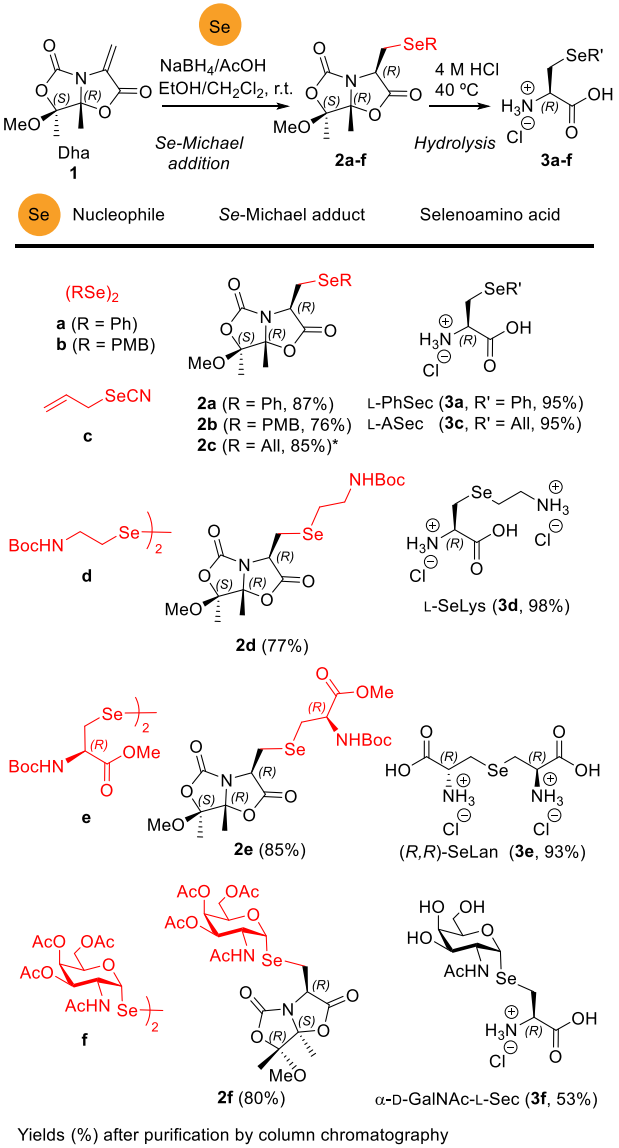
This preliminary result was improved using our second generation chiral Dha (**1**),[11c] which showed excellent results in other Michael-type additions,[11d] as the *Se*-Michael acceptor. Thus, using the same conditions described before, complete conversion was achieved in 5 min and a single diastereoisomer **2a** was obtained (Scheme 2). Other sources of *Se*-nucleophiles were assayed, such as benzeneselenol in the presence of Al_2O_3 in toluene at room temperature. The conversion was again quantitative, and the same single diastereoisomer **2a** was obtained (Scheme S2 in Supporting Information).

Scheme 2. Stereoselective *Se*-Michael Additions of *Se*-Nucleophiles to Dha 1 and Synthesis of Selenoamino Acids



The absolute configuration of the new stereocenter (C3) of compound **2a** formed in the *Se*-Michael addition was determined by X-ray analysis of monocrystals of this compound (Figure 1). Alternatively, this structural feature was also determined by a 2D NOESY−NMR experiment on **2a** (Supporting Information).

Remarkably, in the *Se*-Michael reactions on Dha **1**, a single diastereomer was observed in the ^{1}H NMR spectrum of the crude reaction mixture, indicating that they occur with complete diastereoselectivity. This stereochemical outcome points to a robust stereoinduction mechanism for the protonation of the enolate adduct formed after conjugate addition, similar to that previously described for *S*-Michael additions[11c] on Dha **1** (Scheme S3 in Supporting Information).

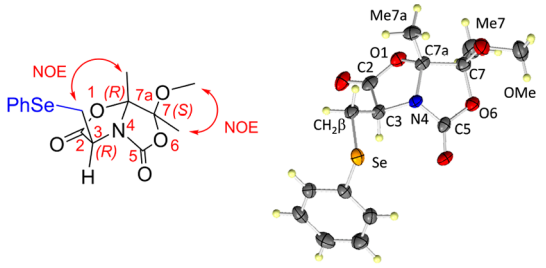


Figure 1. ORTEP diagram of compound **2a**, showing thermal ellipsoids at the 75% probability level.

The scope of the reaction of chiral Dha **1** with several *Se*-nucleophiles was examined under similar conditions. Other sources of selenium nucleophile were explored, but the diselenides in the presence of $NaBH_4$ proved to be more versatile and facilitated workup. We carried out the conjugate additions with a wide variety of reagents leading to motifs that arise in nature via post-translational modifications. In all cases, high yields and diastereoselectivities were achieved and all the 1,4-conjugate adducts (**2a−f**) were obtained as single stereoisomers (Scheme 2). The absolute configuration of the new stereocenters was also determined by 2D NOESY-NMR experiments (Supporting Information), demonstrating that the same stereochemical outcome was achieved for all *Se*-nucleophiles with Dha **1**.

L-Phenylselenocysteine (L-PhSec, **3a**) is an important amino acid used in NCL which together with the corresponding Fmoc-derivative have been prepared by nucleophilic substitution with *Se*-nucleophiles on adequately activated Ser-derivatives.[12] The hydrolysis of *Se*-Michael adduct **2a** with aqueous 4 M HCl at 40 °C yielded enantiomerically pure L-PhSec **3a** in 95% yield (Scheme 2). The stereochemical integrity of the α-carbon was maintained upon deprotection, as verified by their optical properties.[12] Thus, our methodology provides an easy entry to *N*-Fmoc-PhSec[12] (Scheme S4 in Supporting Information) readily available for being used in solid-phase peptide synthesis.

Se-Michael adduct **2b** was easily achieved through 1,4-conjugate addition of di-*p*-methoxybenzyl diselenide, $(PMBSe)_2$, **b** to Dha **1** in the presence of $NaBH_4$ (Scheme 2). In this case, the acid hydrolysis of the corresponding *Se*-Michael adduct **2b** gave enantiopure L-selenocystine **4b** by complete hydrolysis of all the protecting groups including PMB[13] and in situ oxidation of the corresponding L-Sec (Scheme 2 and Scheme 3).

Selenium exerts chemopreventive activity against several types of cancer.[14] Its biologic activity is related to its incorporation in a diversity of biochemical forms. For instance, *Se*-allylselenocysteine (abbreviated as ASC, Seac or Asec, **3c**) is an effective metabolite in inhibiting mammary carcinogenesis, but its role of cytotoxicity in chemoprevention is unknown.[14] In addition, Asec allowed site-specific incorporation of Sec in proteins.[7a] Using our methodology, the *Se*-Michael addition to Dha **1** was carried out with allylselenocyanate **c** and $NaBH_4$

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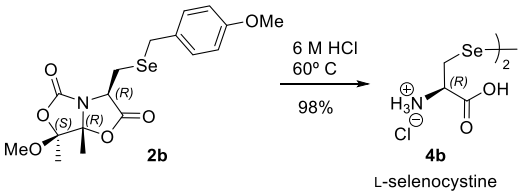
Scheme 3. Synthesis of L-Selenocystine 4b



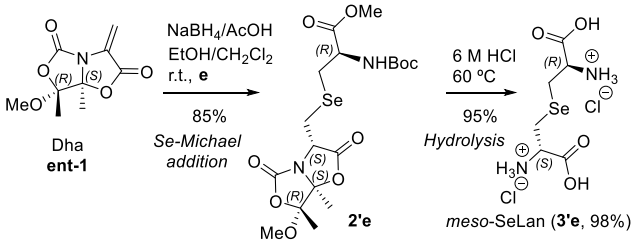
generating the corresponding adduct **2c** with a good yield and stereoselectivity. In this case, ^{i}PrOH was used as a cosolvent instead of EtOH to avoid the formation of byproducts arising from the nucleophilic attack of EtOH to the lactone of *Se*-Michael adduct **2c** (Scheme S5 in Supporting Information). This adduct **2c** was hydrolyzed to give L-Asec (**3c**), whose physical properties match those described in the literature[7a,10] (Scheme 2).

Recently, selenium-containing analogues of modified Lys residues have been developed in order to facilitate traceless isopeptide bond formation through isopeptide chemical ligation.[15] In addition, it is well-known that 4-selenalysine (SeLys) has been used as a substitute for Lys to synthesize artificial lanthipeptides from in vitro translation.[16] In general, the introduction of selenium in the skeleton of amino acid involves the use of disodium diselenide and *tert*-butyl (2-chloroethyl)carbamate to obtain the respective selenium-based nucleophile di-*tert*-butyl (diselanediylbis(ethane-2,1-diyl))-dicarbamate, which is able to react in situ through an S_N2 reaction with *N*-Boc-*β*-bromoalanine methyl ester giving the corresponding protected SeLys. As an alternative, we carried out the stereoselective synthesis of L-SeLys (**3d**) by *Se*-Michael addition of di-*tert*-butyl (diselanediylbis(ethane-2,1-diyl))-dicarbamate **d** to Dha **1** followed by acid hydrolysis (Scheme 2).

Selenolanthionine (SeLan) was selected as another selenoamino acid target for our methodology. Several reports[17] described the synthesis of SeLan, including its incorporation in lanthipeptides,[18] with a renewed interest.[19] Optically active (*R*,*R*)-SeLan was synthesized by reacting Dha **1** with the selenolate derivative of Boc-L-Sec-OMe, which was in situ generated from Boc-L-selenocystine-OMe **e** by the action of $NaBH_4$, to give *Se*-Michael adduct **2e** with a 85% yield and high diastereoselectivity (Scheme 2). In the same way, the *Se*-Michael reaction of **e** with the enantiomer of Dha **1** (**ent-1**) yielded adduct **2′e**. (Scheme 4). Both adducts **2e** and **2′e** were hydrolyzed to give (*R*,*R*)-SeLan **3e** (Scheme 2) and *meso*-SeLan **3′e** in high yields and diastereomeric purities, respectively (Scheme 4).

Recently, a *Se*-mimetic of the Tn antigen derived from Thr [*Se*-(*α*-D-GalNac)-L-selenothreonine, abbreviated as *α*-D-GalNac-L-*Se*Thr] has been reported.[20] Such a Tn antigen mimetic showed improved antibody recognition properties when incorporated into a peptide sequence as a result of optimized peptide/carbohydrate interactions resulting from an O/Se replacement at the glycosidic linkage. As an entry to diastereopure Se-Tn mimetics, we assayed the reaction of diselenosugar **f** with Dha **1**, following the conditions described in Scheme 2, to give adduct **2f** as a single diastereoisomer, whose stereochemistry was determined by NOE experiments. Diselenosugar **f** was prepared from a peracetylated GalNAc derivative following the methodology previously described by us.[20] *Se*-Michael adduct **2f** was hydrolyzed in an acidic medium to give Tn antigen mimetic *α*-D-GalNac-L-Sec **3f** (Scheme 2).

Scheme 4. Synthesis of *meso*-SeLan 3′e



In conclusion, this work describes the first totally chemo- and stereoselective 1,4-conjugate additions of different *Se*-nucleophiles to chiral bicyclic dehydroalanine (Dha) **1**. The reactions are carried out using a general, mild, and noncatalytic methodology and provide good to excellent yields. *Se*-nucleophiles are generated in situ from the corresponding stable and easily accessible or commercially available diselenide derivatives, by the action of sodium borohydride. Simple acidic hydrolysis of the corresponding adducts gives access to a small collection of enantiopure Sec derivatives, such as L-PhSec, L-selenocystine, L-ASec, L-SeLys, (*R*,*R*)- and *meso*-SeLan, and Tn antigen mimetic *α*-*Se*-GalNAc-L-Sec. In fact, our methodology comprises a new strategy for the emerging field of stereoselective *Se*-glycosylation.[21] In summary, readily available starting materials, mild conditions, functional group tolerance, and high yields and stereoselectivities make this strategy an appealing method for the synthesis of enantiomerically pure selenoamino acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03832.

Experimental procedures, characterization data, and copies of the NMR spectra (PDF)

Crystallographic data (TXT)

Accession Codes

CCDC 2045571 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 Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors./All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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