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# Combining spiro-fused cyclohexadienone ─ tetrahydrofuran ring system with glycine: Asymmetric synthesis of a new class of α-amino acid derivatives

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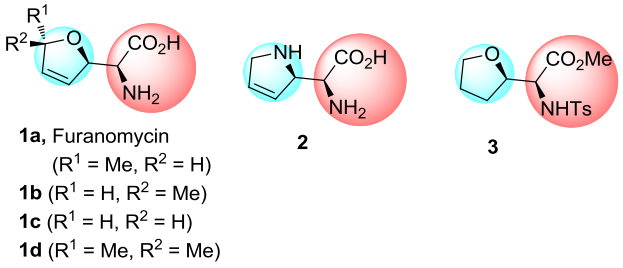
ABSTRACT

Herein, we present the asymmetric synthesis of spiro-fused cyclohexadienone ─ tetrahydrofuran-embedded glycine derivatives as a new class of nonproteinogenic α-amino acid derivatives. Starting from commercially available 2-allylphenols, key β-hydroxy-α-amino esters were synthesized via high-yielding multi-step reaction sequences involving Sharpless asymmetric dihydroxylation as the chirality induction step. PhI(OAc)$_2$-mediated oxidative dearomatization ─ spirocyclization of phenol-tethered β-hydroxy-α-amino esters efficiently produced the corresponding spiro-fused cyclohexadienone ─ tetrahydrofuran-embedded glycine derivatives, providing a general route to this hitherto-unreported class of compounds that are equipped with three privileged scaffolds (cyclohexadienone ─ tetrahydrofuran ─ α-amino ester).



The past few decades have witnessed tremendous exploitation of nonproteinogenic α-amino acids in the construction of designer peptides and proteins.[1] The utilization is largely attributed to the fact that incorporation of such amino acids into peptides/proteins can alter the chemical, biophysical, and pharmacokinetic properties of the latter compounds. The worth of nonproteinogenic α-amino acids in organic/medicinal chemistry is further enriched by their utility as building blocks in the synthesis of diverse biologically active (non-peptide) compounds, organocatalysts, chiral ligands and auxiliaries.[2] Tremendous advances have already been made in the stereoselective synthesis of large number of nonproteinogenic α-amino acids. For the full potential of this class of compounds to be realized in the above-mentioned applications, however, it is necessary to expand the pool of existing α-amino acids. Thus, to broaden the diversity, it is highly desirable to synthesize new varieties of α-amino acids, particularly those bearing a heterocycle moiety.

L-(+)-Furanomycin (**1a**, Figure 1) is a natural α-amino acid that was first isolated by Katagiri *et al.* in 1967 from the fermentation broth of *Streptomyces threomyceticus*.[3] This nonproteinogenic α-amino acid acts as a competitive antagonist of isoleucine and suppresses the growth of several bacterial species such as *E. coli*, *Bacillus subtilis*, or *Shigella* and *Salmonella* strains.[3] It suppresses the growth of T-even coliphage more effectively than T-odd.[3] Subsequent studies have demonstrated that furanomycin binds to *E. coli* isoleucyl-tRNA synthetase to be incorporated into a protein.[4] Due to these important biological activities, several studies detailing the racemic and asymmetric total synthesis of furanomycin and its analogues/derivatives such as **1b-d**, **2** and **3** have appeared in the literature over the last 30 years.[5]




**1a,** Furanomycin ($R^1$ = Me, $R^2$ = H)
**1b** ($R^1$ = H, $R^2$ = Me)
**1c** ($R^1$ = H, $R^2$ = H)
**1d** ($R^1$ = Me, $R^2$ = Me)

**2**

**3**

**Figure 1.** Furanomycin and its analogs/derivatives.

On the other hand, spirocyclohexadienones, containing a quaternary or fully substituted carbon center, are present as substructures in many bioactive natural products, pharmaceuticals, and compounds for diverse other applications.[6] Among the many classes of spirocyclohexadienones, the spiro-fused cyclohexadienone ─ tetrahydrofuran (SFCT) system is an interesting structural motif found in the natural products aculeatins A–D (Figure 2, upper panel) which exhibit antimalarial activity against the P. *falciparum* 3D7 strain.[7,8]

The research in our group has been focused on the stereoselective synthesis of oxygen heterocycles.[9] Knowing the biological importance of SFCT system, and drawing inspiration from the literature reports describing the synthesis of furanomycin and related compounds, we targeted SFCT systems bearing glycine derivative **5** (Figure 2, lower panel). It is important to mention that during the past decades, diverse SFCT systems have been reported[7,8] ─ but those bearing an α-amino acid derivative moiety like **5** have never been synthesized. Such hybrid compounds bearing three different well-known structural

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units (cyclohexadienone – tetrahydrofuran – α-amino acid) might be useful in the drug discovery process. Herein, we describe our preliminary efforts that were made to stereoselectively synthesize **5**.

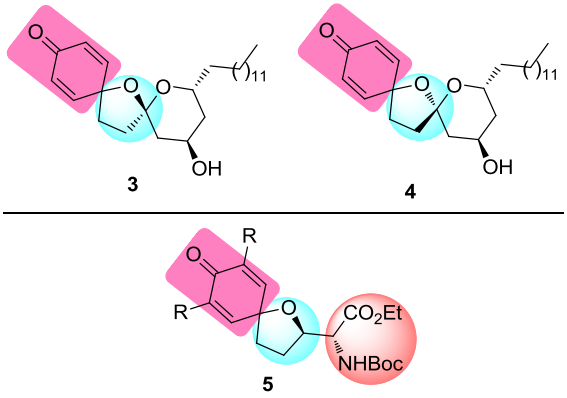
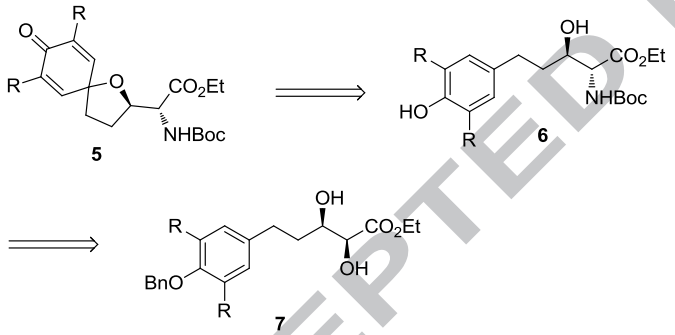



**Figure 2.** Selected natural products containing SFCT system (upper panel) and our target hybrid nonproteinogenic α-amino acids.

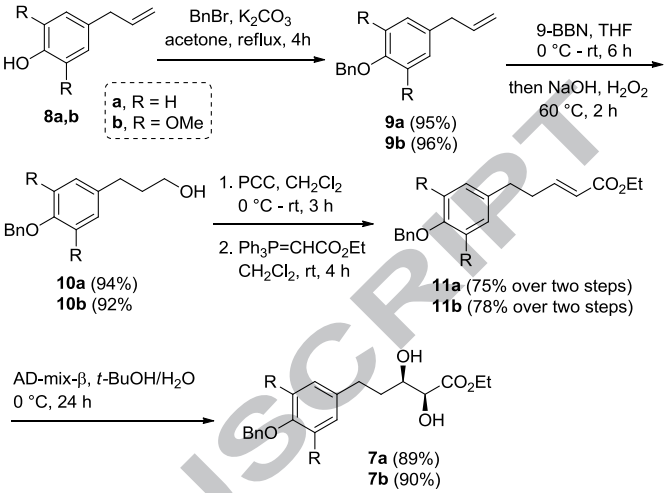
In our retrosynthetic design, the target compounds 5 could be constructed via oxidative dearomaziation – regioselective spirocyclization of **6**. β-Hydroxy-α-(protected)amino ester **6** was expected to be synthesized via regioselective functional group transformations of the α-OH of Sharpless asymmetric dihydroxylation-derived α,β-dihydroxy esters **7**.[10]




**Scheme 1.** Retrosynthesis of SFCT bearing nonproteinogenic α-amino acids.

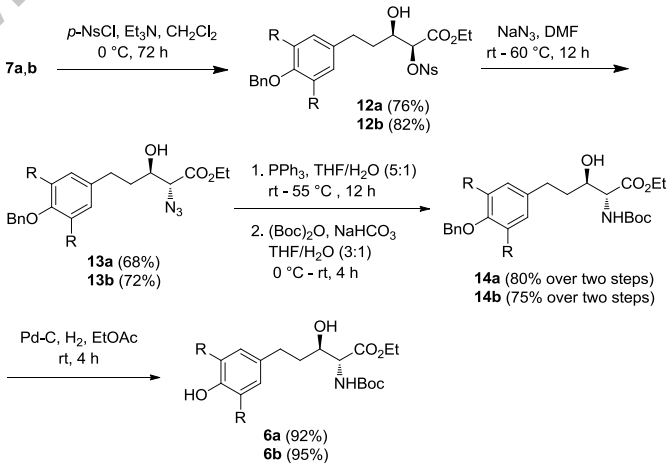
As shown in Scheme 2, we first set out to synthesize enantiomerically pure α, β-dihydroxy esters **7a** and **7b** that would be used as starting materials for the synthesis of β-hydroxy-α-(protected)amino ester **6**. Compounds **7a** and **7b** were conveniently prepared in from commercially available 4-allylphenols **8a** and **8b**, respectively. Thus, benzylation of **8a** and **8b** with BnBr in the presence of $K_2CO_3$ followed by hydroboration (9-BBN)–oxidation ($H_2O_2$, NaOH) of the resulting compounds **9a**,**b** gave primary alcohols **10a** and **10b**, respectively. PCC oxidation of **10a**,**b** followed by Wittig olefination of the resulting crude aldehydes with $Ph_3P{=}CHCO_2Et$ furnished **11a** and **11b**, respectively. Dihydroxylation of **11a**,**b** under the Sharpless asymmetric dihydroxylation conditions (AD mix β) provided α, β-dihydroxy esters **7a** (ee: 96.2%) and **7b** (ee: 95.1%), respectively.[11]

Next, regioselective mononosylation of **7a**,**b** followed by azidation of the resulting β-hydroxy-α-nosyloxy esters **12a**,**b** with $NaN_3$ afforded β-hydroxy- α-azido esters **13a** and **13b**, respectively (Scheme 3). Subsequent attempted one-pot debenzylation-azide reduction-*N*-Boc protection of **13a** and **13b** to provide **6a**,**b** under standard debenzylation conditions (Pd-C, $H_2$) and in the presence of $(Boc)_2O$ was unsuccessful (not shown here).




**Scheme 2.** Synthesis of precursor diols.

Consequently, a stepwise protocol was followed. Thus, Staudinger reduction ($PPh_3$, THF, $H_2O$) of **13a**,**b** followed by N-Boc protection of the resulting crude amines yielded N-Boc-protected β-hydroxy- α-amino esters **14a** and 1**4b**, respectively. Finally, compounds **14a**,**b** were subjected to debenzylation with Pd-C and $H_2$ to afford phenols **6a** and **6b**, respectively.

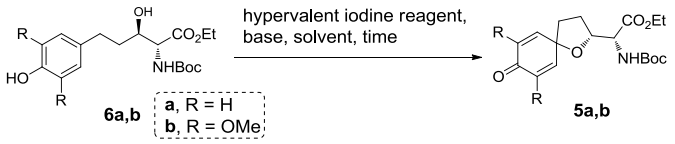



**Scheme 3.** Synthesis of N-Boc-protected β-hydroxy-α-amino esters.

With the key compounds **6a**,**b** in hand, our attention was turned for their conversion to SFCT-embedded glycine esters **5a**,**b**. Toward that objective, we decided to employ hypervalent iodine(III)-based reagents to effect the oxidative dearomatization[12] of **6a**,**b** under six different reaction conditions (Table 1, entries 1-6). Treatment of compounds **6a**,**b** with phenyliodine(III) diacetate (PIDA) in MeCN led to complete consumption of starting materials within 15 min and formation of desired products **5a**,**b**, albeit in very low yields (Table 1, entry 1). The other well-known hypervalent iodine(III) reagent, i.e., phenyliodine(III) bis(trifluoroacetate) (PIFA) in MeCN also furnished similar yields (entry 2). With PIDA and PIFA as the oxidizing agents, the screening showed that the reaction gave better yields in trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) (entries 3-6). Compared to their non-fluorinated alcohol analogues, TFE and HFIP have low pKa, low nucleophilicity, and very high ionizing power.[13] These are major stabilizing

factors for the intermediate phenoxenium cation formed during an oxidative dearomatization process mediated by hypervalent iodine(III) ragents.[14] Thus, the higher yields in TFE and HFIP compared to that in acetonitrile were not surprising. Nevertheless, this transformation was best carried out using PIDA as an oxidizing agent and $K_2CO_3$ as a base in HFIP (entry 5). It is important to mention that Boc group was not affected by HFIP which has been reported to cause Boc deprotection, albeit under much harsher reaction conditions (compared to the conditions described in Table 1).[15]

**Table 1**. Screening of reaction conditions on the oxidative dearomatization ─ regioselective spirocyclization of **6a**,**b**[a]




| entry | conditions[a] | yield[a] |
|---|---|---|
| 1 | PIDA, $K_2CO_3$, MeCN | 27% (**5a**); 36% (**5b**) |
| 2 | PIFA, pyridine, MeCN | 29% (**5a**); 35% (**5b**) |
| 3 | PIDA, $K_2CO_3$, TFE | 52% (**5a**); 55% (**5b**) |
| 4 | PIFA, pyridine, TFE | 55% (**5a**); 59% (**5b**) |
| 5 | PIDA, $K_2CO_3$, HFIP | 65% (**5a**); 62% (**5b**) |
| 6 | PIFA, $K_2CO_3$, HFIP | 57% (**5a**); 58% (**5b**) |

[a]Reaction conditions: **6a** or **6b** (0.1 mmol), $K_2CO_3$ (0.12 mmol) or pyridine (0.2 mL), solvent (2 mL) at 0 °C – rt for 15 min (for entries 1 and 2) or 10 min (for entries 3-6) . [b]Isolated yields after column chromatography.

Notably, the oxidative dearomatization ─ spirocyclization was completely regioselective as we could not find even any trace of the corresponding spiro-fused cyclohexadienone ─ piperidine ring system which might arise due to the nucleophilic attack of the NHBoc group (instead of the –OH group). The synthesis involves a total of 12 linear steps for each of **5a** and **5b**. Further diversification (ring size and substituents) of this methodology along with its relevant synthetic and medicinal applications is underway in our laboratory and will be reported in due course as a full paper.

In summary, we have described our preliminary efforts toward the synthesis of spiro-fused cyclohexadienone ─ tetrahydrofuran containing glycine derivatives for which we chose Sharpless asymmetric dihydroxylation as the source of chirality and PIDA-mediated oxidative dearomatization ─ regioselective spirocyclization as the key step. Owing to the ease with which the starting materials for the oxidative dearomatization-spirocyclization could be made, as well as the high derivatizability of a spirocyclohexadienone moiety, this synthetic route should be useful as a general route to wide varieties of related unnatural α-amino acid derivatives.

## Acknowledgments

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## Supplementary Material

Experimental procedures, characterization data and copies of $^1H$ and $^{13}C$ NMR spectra for final compounds are available.

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## Graphical Abstract

**Combining spiro-fused cyclohexadienone – tetrahydrofuran ring systems with glycine: Asymmetric synthesis of new classes of α-amino acid derivatives**

Runjun Devi and Sajal Kumar Das*

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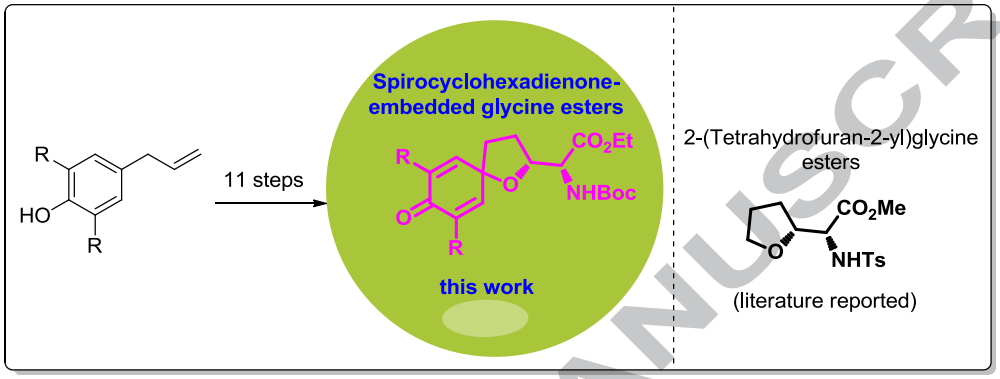

**Highlights**

- Synthesis of spirocyclohexadienone bearing glycine derivatives has been achieved.
- They represent a new class of unnatural α-amino acid derivatives.
- Sharpless asymmetric dihydroxylation was employed as the source of chirality.
- Key step involved phenyliodonium diacetate-induced dearomatizing spirocyclization