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Synthesis of 2-Substituted-5-halo-2,3-dihydro-4(*H*)-pyrimidin-4-ones and Their Derivatization Utilizing the Sonogashira Coupling Reaction in the Enantioselective Synthesis of α-Substituted *β*-Amino Acids

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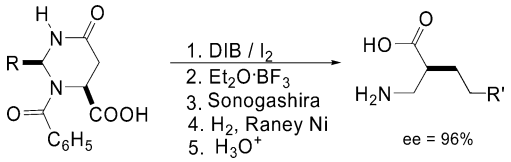

A convenient, one-pot procedure for the synthesis of 1-benzoyl-2(*S*)-substituted-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-ones by tandem decarboxylation/*β*-iodination of the corresponding 6-carboxy-perhydropyrimidin-4-ones was developed. In addition, several 1-benzoyl-2(*S*)-substituted-5-bromo-2,3-dihydro-4(*H*)-pyrimidin-4-ones were readily prepared by bromination of 1-benzoyl-2(*S*)-substituted-2,3-dihydro-4(*H*)-pyrimidin-4-ones. Subsequently, Sonogashira coupling of the halogenated heterocyclic enones with various terminal alkynes produced 1-benzoyl-2(*S*)-isopropyl-5-alkynyl-2,3-dihydro-4(*H*)-pyrimidin-4-ones in good yields. Hydrogenation of the unsaturated C−C moieties in the Sonogashira products followed by acid hydrolysis afforded highly enantioenriched α-substituted *β*-amino acids.

Introduction

Perhydropyrimidinone carboxylic acid (2*S*,6*S*)-**1a** has been used as an efficient starting material for the enantioselective synthesis of (*R*)- and (*S*)-α-substituted[1] and α,α-disubstituted *β*-amino acids.[2] Furthermore, several analogues of pyrimidinone (*S*)-**2** have proven useful for the asymmetric synthesis of *β*-substituted, α,*β*-disubstituted, and *β*,*β*-disubstituted *β*-amino acids (Scheme 1).[3]

Recently, we reported that treatment of carboxylic acid (2*S*,6*S*)-**1a** with diacetoxyiodobenzene/iodine (DIB/I_2)[4] afforded a 1.6:1.0 mixture of the iodoenone (*S*)-**3a** and the enone (*S*)-**4a**.[5] The finding that iodoenone (*S*)-**3a** is cleanly converted into enone (*S*)-**4a** upon treatment with iodotrimethylsilane (generated with chlorotrimethylsilane and sodium iodide) (Scheme 2a) led to the development of a one-pot protocol involving decarboxylation, *β*-iodination, and hydrodeiodination of (2*S*,6*S*)-**1a** to give (*S*)-**4a** in 71% yield (Scheme 2b).[6]

Nevertheless, in view of the structural similarity between 5-iodopyrimidinone (*S*)-**3a** and various 5-halouracils showing

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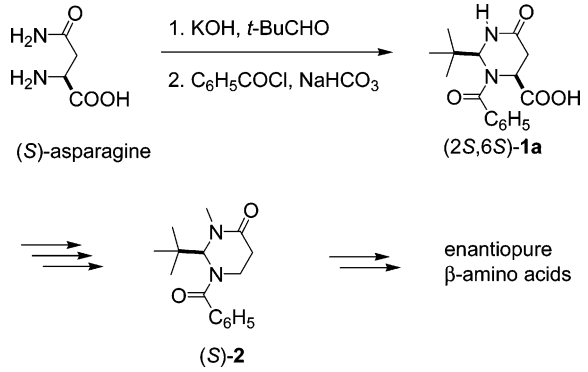
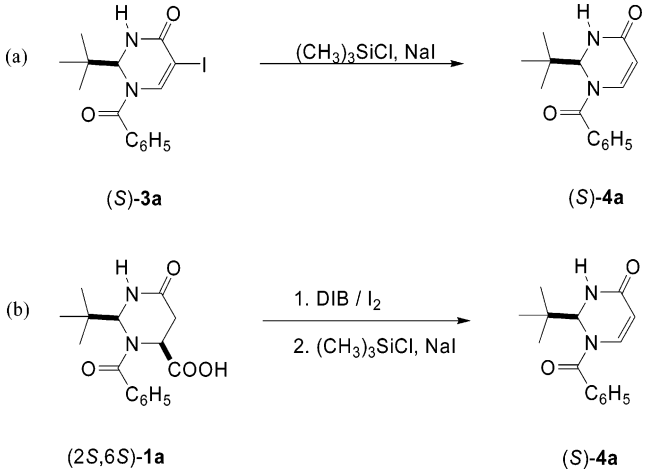
SCHEME 1. Enantioselective Synthesis of β-Amino Acids via Chiral Pyrimidinones



SCHEME 2. Preparation of Enone (*S*)-4a



antiviral activity (Figure 1),[7] we sought to develop reaction conditions for the decarboxylation/β-iodination of (2*S*,6*S*)-**1a** to provide (*S*)-**3a** as the single product.

The structural similarity of haloenones **3** and 5-halouracils (Figure 1) suggested that they should present the same chemical reactivity. For example, there are successful reports of the application of Sonogashira couplings to substitute the halogen in 5-halouracils.[8] Thus, compounds (*S*)-**3** presented themselves as interesting substrates for this kind of coupling. Furthermore, the expected products could prove to be suitable precursors to enantiomerically pure β-amino acids.[9]

Results and Discussion

Diastereomerically pure perhydropyrimidinone-6-carboxylic acids **1a**−**c** were prepared by condensation of (*S*)-asparagine with pivalaldehyde, isobutyraldehyde, or benzaldehyde, respectively, followed by in situ N-benzoylation[3a,10] (Scheme 3).

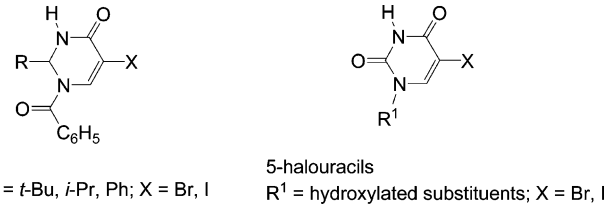


FIGURE 1. Structural similarity between haloenones **3** and biologically relevant 5-halouracils.

Treatment of perhydropyrimidinone-6-carboxylic acids **1a**−**c** with DIB (2 equiv) and iodine (1 equiv) in CH_2Cl_2 during 4.5 h afforded a mixture of the expected[5] enones **4** and iodoenones **3** (cf. Scheme 2). We were pleased to find that addition of $BF_3 \cdot Et_2O$ (2 equiv) to the resulting reaction mixture resulted in the fast conversion of the enone into the corresponding iodoenone, which becomes the sole reaction product (Scheme 3).

Because acetic acid is formed in the reaction medium upon reduction of DIB, it is likely that acetic acid reacts with the DIB/I_2 reagent to produce acetyl hypoiodite,[11] which is activated by BF_3 to liberate iodonium ion (Scheme 4a). Finally, iodonium ion adds to enones **4** to give, after β-elimination of a proton, the desired iodoenones **3** (Scheme 4b).

In addition, bromoenones **5a**−**c** were prepared from enones **4a**−**c** by bromination with pyridine perbromide hydrobromide ($Pyr \cdot HBr \cdot Br_2$)[12] (Scheme 5). The mechanism for the bromination reaction is anticipated to be similar to that presented in the iodination reaction (cf. Scheme 4b), with bromonium, Br^+, instead of iodonium ion.

Crystals of (*S*)-**5b** were obtained by recrystallization from CH_2Cl_2 and ethyl acetate, and the crystal structure was determined by X-ray diffraction crystallography (Figure 2, Supporting Information).

For the preparation of bromoenones **5a**−**c** (Scheme 5), starting enones **4a**−**c** were prepared in good yields following our recently reported decarboxylation/β-iodination/hydrodeiodination tandem protocol (**1a**−**c** → **4a**−**c**, cf. Scheme 2b).[6] A single crystal of 1-benzoyl-2(*S*)-phenyl-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-**4c**, could be obtained, and Figure 3 (Supporting Information) shows its molecular structure.

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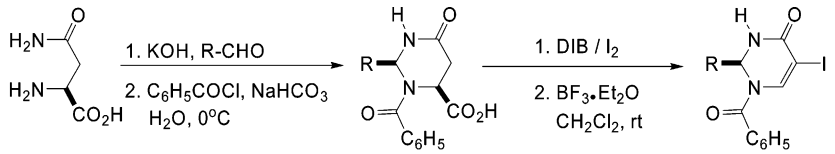
SCHEME 3. Preparation of Enantiopure Iodoenones 3a−c

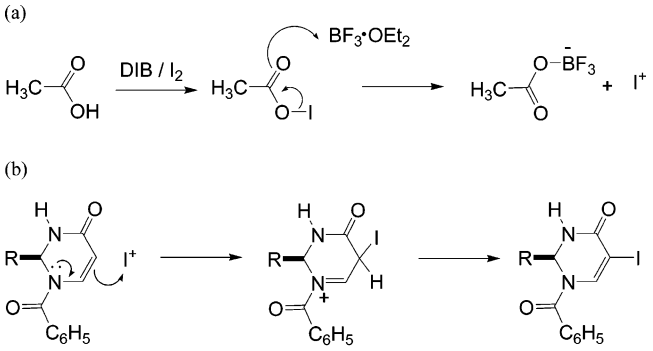


(*S*)-asparagine

1a, (2*S*, 6*S*), R = $(CH_3)_3C$, 71%
1b, (2*S*, 6*S*), R = $(CH_3)_2CH$, 68%
1c, (2*S*, 6*S*), R = C_6H_5, 15%

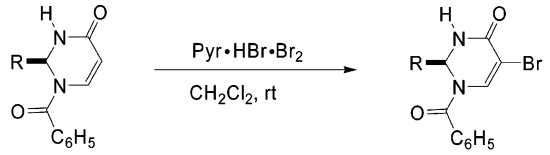
3a, (*S*), R = $(CH_3)_3C$, 56%
3b, (*S*), R = $(CH_3)_2CH$, 78%
3c, (*S*), R = C_6H_5, 59%

SCHEME 4. Proposed Mechanism in the Iodination Reaction of Enones 4



4 **3**

SCHEME 5. Bromination of Enones 4a−c with Pyridine Perbromide Hydrobromide



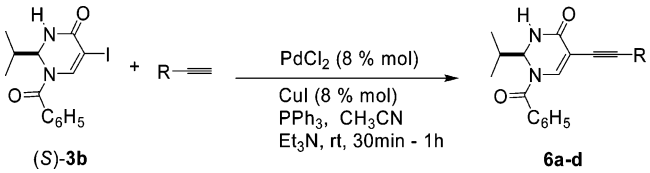
4a, (*S*), R = $(CH_3)_3C$
4b, (*S*), R = $(CH_3)_2CH$
4c, (*S*), R = C_6H_5

5a, (*S*), R = $(CH_3)_3C$, 69% yield
5b, (*S*), R = $(CH_3)_2CH$, 79% yield
5c, (*S*), R = C_6H_5, 90% yield

Finally, compounds **6a−d** were obtained by Sonogashira coupling.[13] The reaction proceeded satisfactorily using iodoenone (*S*)-**3b** and terminal alkynes (phenylacetylene, propargylic alcohol, 1-heptynyl, and 1-hexynyl) in the presence of triethyl amine, PPh_3, CuI, and with $PdCl_2$ as catalyst in acetonitrile. The coupling was carried out at room temperature, and the isolated yields obtained varied in the 59−88% range (Table 1).

Following recrystallization of compound (*S*)-**6a**, good crystals were obtained, and the corresponding X-ray crystallographic structure is shown in Figure 4 (Supporting Information). As also shown in the X-ray crystallographic structures of compounds **4c**, **5b**, and **6a** (Figures 2−4, Supporting Information), the six-membered heterocycles adopt conformations that approach a sofa.[14] The near-planarity among the N(3), C(4), C(5), C(6), and N(1) atoms is due to conjugation of the α,*β*-unsaturated amides.

TABLE 1. Sonogashira Reaction of Iodoenone (*S*)-3b and Terminal Alkynes



(*S*)-**3b** **6a-d**

entry	R	product	mp (°C)	$[\alpha]^{25}_D$	yield (%)
1	C_6H_5	**6a**	249−251	+652.8	88
2	$CH_2(CH_2)_3CH_3$	**6b**	157−158	+543.0	76
3	$CH_2(CH_2)_2CH_3$	**6c**	129−131	+538.0	82
4	CH_2OH	**6d**	187−189	+594.5	59

Hydrogenation and Hydrolysis of the Sonogashira Products To Afford Highly Enantiomerically Enriched α-Substituted *β*-Amino Acids. Hydrogenation of the unsaturated C−C segments in the Sonogashira product **6a** was then attempted under various conditions ($NiCl_2 \cdot 6H_2O/NaBH_4$,[15] Mg/$ZnCl_2$,[16] $NaBH_3CN$,[17] Zn/AcOH,[18] Li/NH_3, Mg/CH_3OH[19]) without success. By contrast, hydrogenation catalyzed with Rh-alumina, Ni-alumina, Pt, and Pd/C afforded (*S*)-**7**, originating from exclusive reduction of the side chain, as the main product (Scheme 6).

Hydrogenation of the endocyclic double bond in alkylated enone (*S*)-**7** with H_2/Raney Ni/AcOH/CH_3OH provided epimers (2*S*,5*S*)-**8** and (2*S*,5*R*)-**8**, with the former product always predominating as anticipated in terms of a more facile approach

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SCHEME 6. Catalytic Hydrogenation of Sonogashira Products

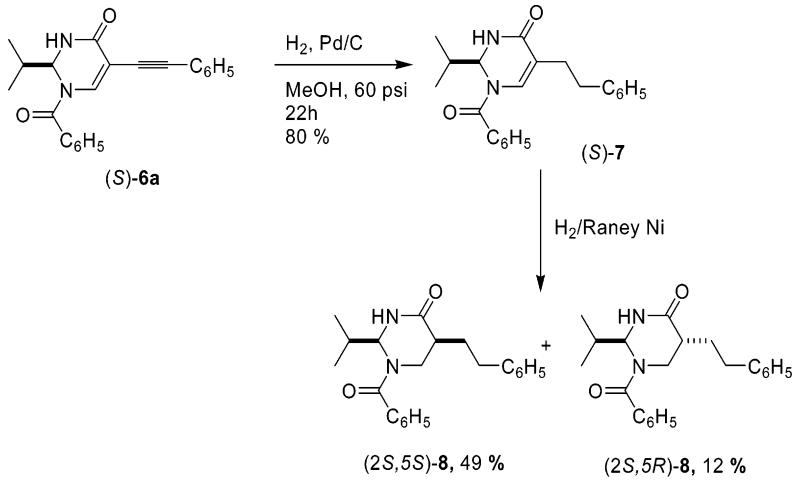
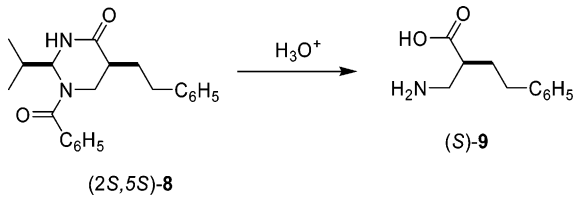


TABLE 2. Acid-Catalyzed Hydrolysis of (2*S*,5*S*)-8 in the Preparation of (*S*)-2-(Aminomethyl)-4-phenylbutanoic Acid, (*S*)-9



entry	reaction conditions	reaction time (h)	temp (°C)	acid	yield (%)	ee (%)[a]
1	sealed tube	6	90	48% HBr	40	72
2	sealed tube	6	90	6N HCl	18	88
3	sealed tube	12	90	6N HCl	51	80
4	MW, 35−40 W, no air cooling	6	100	6N HCl	45	82
5	MW, 100 W, air cooling	12	95−100	6N HCl	66	84
6	MW, 150 W, air cooling	6	120	6N HCl	53	88
7	**MW, 100 W, air cooling**	**6**	**80−88**	**6N HCl**	**24**	**96**
8	MW, 100 W, air cooling	12	80−86	6N HCl	45	90
9	MW, 200 W, air cooling	6	80−88	6N HCl	81	86
10	**MW, 200 W, air cooling**	**6**	**98**	**4N HCl**	**66**	**96**
11	MW, 150 W, air cooling	6	82−88	6N HCl	80	88

[a] Determined by chiral HPLC (Chirobiotic T column, methanol/H_2O (80:20), 1 mL/min).

of the reducing agent from the face of the double bond opposite the isopropyl group[1−3] (Scheme 6).

The two-step hydrogenation [H_2/Raney Ni] of (*S*)-**6a** to give epimers (2*S*,5*S*)-**8** and (2*S*,5*R*)-**8** (Scheme 6) can also be done in a single step, although the yields were somewhat lower, 40% and 6% of (2*S*,5*S*)-**8** and (2*S*,5*R*)-**8,** respectively.

The major product (2*S*,5*S*)-**8** was purified by flash chromatography and exposed to a variety of hydrolytic conditions under acid catalysis (Table 2). It was observed that while conventional heating in a Thermoline apparatus (sealed tube) caused partial racemization of the desired α-substituted *β*-amino acid (entries 1−3 in Table 2), exposure of (2*S*,5*S*)-**8** to 6N HCl during 6 h under microwave irradiation (100 W) at 80−88 °C (temperature controlled with air) afforded (*S*)-2-(aminomethyl)-4-phenylbutanoic acid, (*S*)-**9**, with 96% ee but in low yield (entry 7 in Table 2). We were gratified to find that product (*S*)-**9** was obtained with similar 96% enantiomeric excess but in a better yield (66%) when increased power (200 W) microwaves and lower concentration of the HCl (4N) were used (entry 10 in Table 2). Attemped recrystallization of (*S*)-**9** to increase its stereochemical purity was unsuccessful.

In summary, efficient and simple procedures for the preparation of 2(*S*)-substituted-5-halopyrimidinones (*S*)-**3a**−**c** are described. Sonogashira coupling of (*S*)-**3b** with various terminal alkynes proceeded in good yields to afford derivatives (*S*)-**6a**−**d**. The potential of these alkylated products as precursors of α-substituted *β*-amino acids was demonstrated by means of Raney Ni-catalyzed hydrogenation of Sonogashira product **6a** followed by acid-catalyzed hydrolysis of the main product (2*S*,5*S*)-**8** to afford highly enantioenriched (*S*)-2-(aminomethyl)-4-phenylbutanoic acid, (*S*)-**9**, in good yield.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra of all compounds described in this article, and selected chiral HPLC chromatograms. X-ray crystallographic parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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