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Alternative procedure for the synthesis of enantiopure 1-benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one, a useful starting material for the enantioselective synthesis of α-substituted β-amino acids

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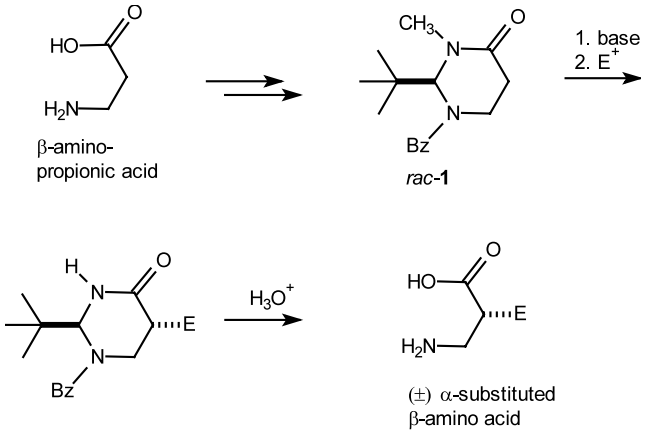
Abstract—The title heterocycle is prepared in enantiomerically pure form and in 46–50% overall yield from (*S*)-asparagine, a readily available starting material. The synthetic route described in this report represents a major improvement over the original procedure (*Tetrahedron: Asymmetry* **1991**, *3*, 723), that afforded a 24–32% overall yield. Furthermore, the use of toxic reagents such as $Pb(OAc)_4$ and dimethyl sulfate is avoided in the present protocol. © 2003 Published by Elsevier Science Ltd.

1. Introduction

The development of synthetic procedures for the preparation of enantiopure β-amino acids has received considerable attention in the recent past.[1] In 1991, β-aminopropionic acid was converted into chiral pyrimidinone *rac*-**1**, that was alkylated with high diastereoselectivity, setting the basis for the enantioselective synthesis of α-substituted β-amino acids[2] (Scheme 1).



Scheme 1.

Indeed, enantiopure pyrimidinone (*S*)-**1** was then prepared from (*S*)-asparagine (Scheme 2),[3] and used as an efficient starting material for the enantioselective synthesis of (*R*)- and (*S*)-α-substituted,[4] and α,α-disubstituted β-amino acids.[5] Furthermore, several analogues of pyrimidinone (*S*)-**1** have proven useful for the asymmetric synthesis of β-substituted, α,β-disubstituted, and β,β-disubstituted β-amino acids.[6]

Replacement of butyllithium and methyl iodide for sodium hydroxide and dimethyl sulfate in the *N*-methylation step [(*S*)-**3**→(*S*)-**4**] led to a significant improvement in the overall yield for the preparation of (*S*)-**1**.[7] Nevertheless, to avoid the use of toxic lead tetraacetate in the decarboxylation reaction [(2*S*,6*S*)-**2**→(*S*)-**3**], we have explored the use of diacetoxyiodobenzene/iodine (DIB/I_2)[8] for the oxidative decarboxylation of carboxylic acid (2*S*,6*S*)-**2**.[9,10] In addition, we have found that *N*-methylation [(*S*)-**3**→(*S*)-**4**] can be conveniently carried out with lithium diisopropylamide and methyl iodide, avoiding the employment of toxic dimethyl sulfate.

2. Results and discussion

Treatment of carboxylic acid (2*S*,6*S*)-**2** with DIB/I_2 gave a mixture of pyrimidinone (*S*)-**3** and the vinylic iodide (*S*)-**5** in a 1:1.6 ratio (Scheme 3).[9]

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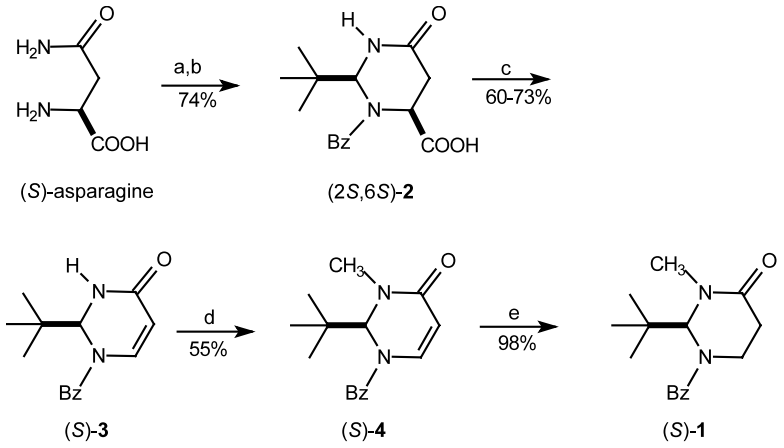
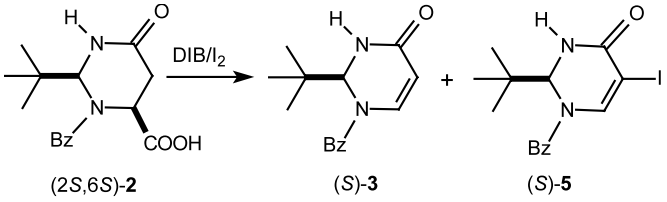
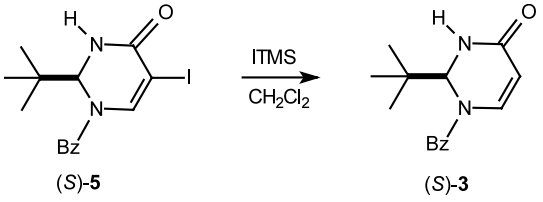


Scheme 2. *Reagents and conditions*: (a) KOH, *t*-BuCHO; (b) C_6H_5COCl, $NaHCO_3$; (c) $Pb(OAc)_4$, $Cu(OAc)_4$ (cat.); (d) *n*-BuLi, CH_3I; (e) H_2, Pd(C), 75 atm.



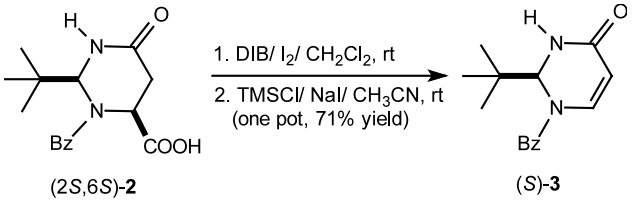
Scheme 3.

As reported previously,[9] iodoenone (*S*)-**5** was cleanly hydrodeiodinated by treatment with 1.2 equiv. of iodotrimethylsilane (ITMS)[11] to afford enone (*S*)-**3** (Scheme 4).



Scheme 4.

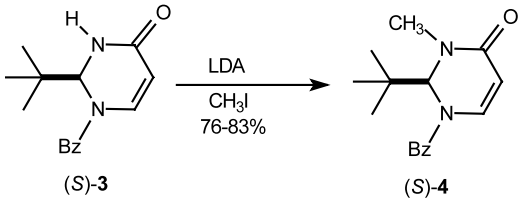
We now have been able to combine the decarboxylation and hydrodehalogenation reactions described in Schemes 3 and 4 into a one pot procedure that is based on the in situ generation of ITMS from chlorotrimethylsilane (TMSCl) and sodium iodide. Thus, treatment of carboxylic acid (2*S*,6*S*)-**2** with two equiv. of DIB and one equiv. of I_2 in CH_2Cl_2, followed by addition of TMSCl (2 equiv.) and NaI (2 equiv.) in CH_3CN, led to the rapid formation of the desired enone (*S*)-**3** in good yield (Scheme 5).



Scheme 5.

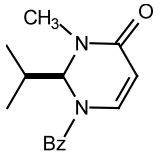
The main advantages of the synthetic protocol described in Scheme 5, relative to the original procedure,[3,7] are: (1) the replacement of toxic lead tetraacetate by safer reagents, (2) the use of milder reaction conditions and shorter reaction times, and (3) the increased facility in the isolation and purification of the desired product, (*S*)-**3**.

N-Methylation of enone (*S*)-**3** was then achieved via a simple and clean procedure involving lithium diisopropylamide (LDA) as base and methyl iodide as electrophile (Scheme 6).



Scheme 6.

Modification of the original synthetic protocol (Scheme 1) by incorporation of the procedures described in Schemes 5 and 6 allows conversion of (*S*)-asparagine into pyrimidinone (*S*)-**1** with and overall yield of 46–50%. This synthetic route has also been applied to the preparation of the isopropyl analog (*S*)-**6**.



3. Experimental

3.1. General

TLC, F_{254} silica gel plates, detection by UV light or iodine vapor. Flash column chromatography: silica gel (230–400 mesh). All melting points are uncorrected, ^{1}H NMR spectra: Jeol Eclipse-400 (400 MHz) spectrometer. ^{13}C NMR spectra: Jeol Eclipse-400 (100 MHz) spectrometer. Optical rotations were measured in a Perkin–Elmer model 241 polarimeter, using the sodium D-line (589 nm).

3.2. One-pot decarboxylation procedure in the preparation of 1-benzoyl-2(*S*)-*tert*-butyl-2,3-dihydro-4(*H*)-pyrimidin-4-one, (*S*)-3

A suspension of the carboxylic acid (2*S*,6*S*)-**2**[3,7] (304 mg, 1.0 mmol), diacetoxyiodobenzene[12] (644 mg, 2.0 mmol), and iodine (253 mg, 1.0 mmol) in 10 mL of CH_2Cl_2 was stirred at ambient temperature for 4–4.5 h. Acetonitrile (20 ml), NaI (300 mg 2.0 mmol) and Me_3SiCl (217.3 mg, 2.0 mmol) were added and the resulting dark solution was stirred for 2.5–3 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with four 20-mL portions of 5% aqueous $Na_2S_2O_3$, two 15-mL portions of 5% aqueous $NaHCO_3$ and two 15-mL portions of brine, dried over anh. Na_2SO_4 and evaporated to afford a yellowish syrup that was purified by flash chromatography (hexane–EtOAc, 100:0→50:50) The desired product was isolated in 71% yield (0.18 g) and was identical to the previously described material.[3,7]

3.3. *N*-Methylation reaction in the preparation of 1-benzoyl-2(*S*)-isopropyl-3-methyl-2,3-dihydro-4(*H*)-pyrimidin-4-one, (2*S*)-6

In a 100 mL round-bottomed flask provided with magnetic stirrer was placed 0.63 mL (4.5 mmol) of diisopropylamine dissolved in 15 mL of dry THF. The solution was cooled to −20°C before the addition of 1.75 mL of 2.34 M BuLi (4.1 mmol), and the resulting mixture was stirred at −20°C for 20 min. In a separate 50 mL flask, a solution containing 1.0 g (4.1 mmol) of 1-benzoyl-2(*S*)-isopropyl-2,3-dihydro-4(*H*)-pyrimidin-4-one[13] in 15 mL of dry THF was cooled to −78°C and added to the previously prepared lithium diisopropylamide. The resulting mixture was stirred at −78°C for 30 min, and then 0.39 mL (6.15 mmol) of iodomethane was added. The reaction temperature was allowed to reach 0°C and the reaction mixture was stirred at this temperature for 4 h, before quenching with 3 mL of aqueous saturated ammonium chloride solution. The *N*-methylated product was extracted with three 15-mL portions of ethyl acetate, the combined organic extracts were dried over anh. Na_2SO_4 and concentrated to afford a yellowish solid. Final purification was accomplished by flash chromatography, with EtOAc/hexane (7:3) as eluent. Pure (*S*)-**6** was obtained as a white solid (0.79 g, 76% yield) with mp 99–100°C (lit.[13] mp 103–104°C). $[\alpha]_D^{25} = +499.0$ (*c* 1.0, $CHCl_3$) [lit.[13] $[\alpha]_D^{29} = +509.9$ (*c* 1.0, $CHCl_3$)].

Acknowledgements

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