A Key Intermediate for Irreversible HIV Protease Inhibitors: Synthesis of Optically Pure *N*-Cbz-5*S*-amino-6-phenyl-hex-3*Z*-enoic Acid

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N-Cbz-5*S*-amino-6-phenyl-hex-3*Z*-enoic acid **8** and its derivatives have received considerable attention because of their potential as key intermediates for the preparation of potent and irreversible HIV protease inhibitors such as **1** and **2**.[1,2]

In addition, the en-acid **8** itself or epoxy acid derived from **8** could serve as a new surrogate for amide bond. Therefore, we decided to develop and optimize a synthetic route to en-acid **8**.

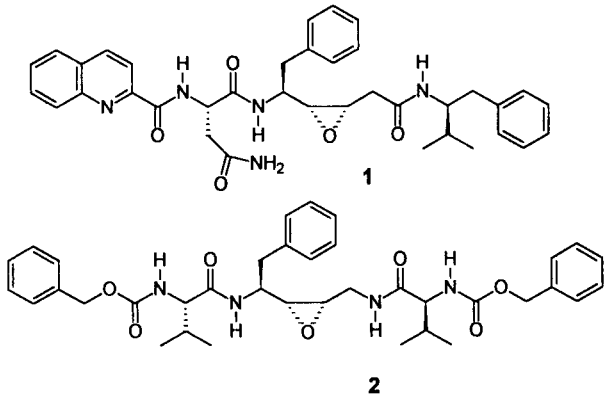
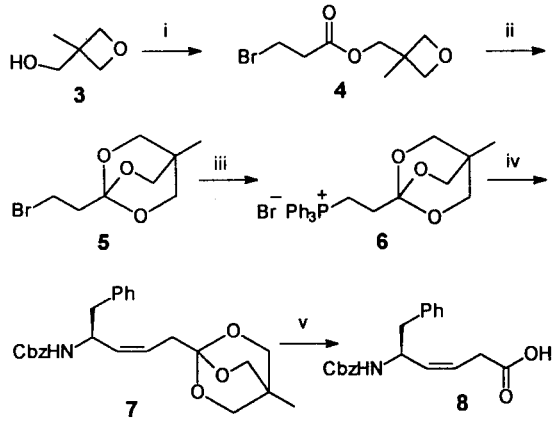
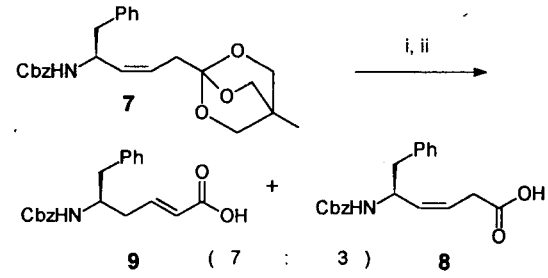


Figure 1. Structures of Irreversible HIV-1 Protease Inhibitors.



Scheme 1. Reagents: i) $BrCH_2CH_2COCl$, pyridine, THF, 0 ℃; ii) BF_3-OEt_2, CH_2Cl_2, Et_3N, 0 ℃; iii) Ph_3P, $NaHCO_3$, CH_3CN, reflux, 48 hrs; iv) $KN(SiMe_3)_2$, THF, −30 ℃ to room temperature; v) 1 N HCl, $^tBuOH/H_2O$, reflux, 10 hrs.



Scheme 2. Reagents: i) 0.3 N H_2SO_4, MeOH; ii) 1 N NaOH.

Results and Discussion

The synthetic route leading to en-acid **8** was outlined in Scheme 1.

As shown, the three-carbon phosphonium salt **6** was prepared in three steps starting from 3-methyl-3-hydroxymethyloxetane. Esterification[3] of the oxetane alcohol **3** with 3-bromopropionyl chloride in THF gave oxetane ester **4**, which was rearranged to the bridged carboxylic orthoester **5** upon treatment with Lewis acid, BF_3-OEt_2. The previous synthesis[3,4] of phosphonium salt involved substitution of bromide by iodide followed by reaction with triphenylphosphine. Since the substitution reaction by sodium iodide afforded moderate yield of the corresponding iodide (49%), the bromide itself was directly subjected to the phosphonium salt formation conditions. Among various conditions attempted, the following reaction condition gave best results: reaction of bromo orthoester **5** with triphenylphosphine in the presence of $NaHCO_3$ in acetonitrile under reflux conditions afforded the phosphonium salt **6** in excellent yield.

Witting reaction of the phosphonium salt **6** with cbz-L-phenylalanal at 80 ℃ using K_2CO_3 as a base afforded 85% yield of olefinic orthoester products **7**. However, the products consisted of a 90 : 10 mixture of the Z and E isomers. In addition, the stereogenic center at the L-phenylalanine moiety was found to be totally racemized. Therefore, a variety of reaction conditions (base, solvent and temperature) were screened to improve the Z/E selectivity and to solve the racemization problem. Conventional bases dimsyl sodium[3] in DMSO or sodium bis(trimethylsilyl)amide[4] in THF were not satisfactory for this specific reaction. Dimsyl anion still caused racemization. While sodium bis(trimethylsilyl)amide afforded a very low yield of the desired product in our hands, potassium bis(trimethylsilyl)amide[5] instead efficiently suppressed racemization, giving high yield of the desired product. Thus, treatment of the cbz-L-phenylalanal with the ylide generated from **6** with KHMDS in THF at −30 ℃ followed by warming the reaction mixture to room temperature cleanly gave **7** in high yield without racemization (Z : E = >99 : 1). Hydrolysis of the olefinic orthoester **7** under the typical reaction condition in the literature[4] gave the more stable α,β-unsaturated acid **9** as a major product (Scheme 2).

The intermediate of the above reaction was methyl ester of **8**, where the source of the methyl group should be methanol. This problem was nicely solved by employing less nucleophilic alcoholic or non-alcoholic solvent such as *t*-BuOH/water, THF/water or dioxane/water. Thus, hydrolysis of the olefinic orthoester **7** in aqeous *t*-butanol instead of

methanol under reflux afforded the desired olefinic acid **8** in high yield.

In summary, we developed an efficient and enantioselective method for the synthesis of *N*-cbz-5*S*-amino-6-phenyl-hex-3*Z*-enoic acid in high yields. This method could be applied to a large scale preparation of the olefinic acid **8** up to a kg scale without any problem.

Experimental Section

General Procedures. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR Spectra were recorded on a Jeol GSX500 spectrometer with chemical shifts expressed in δ units (ppm) relative to tetramethylsilane. FAB Mass spectra were recorded on a Jeol JMS-DX300 Mass Spectrometer. Thin-layer chromatography was conducted with E. Merck silica gel 60 F_{254} plates. Column chromatography was performed using E. Merck silica gel 60 (230-400 mesh). Unless otherwise noted, reactions were conducted under a nitrogen atmosphere.

1-(2-triphenylphosphoniumethyl)-4-methyl-2,6,7-trioxa-bicyclo-[2,2,2]-octane bromide (6). A mixture of bromo orthoester **5** (11.7 g, 50 mmol), triphenylphosphine (19.6 g, 75 mmol) and sodium bicarbonate (5.0 g, 60 mmol) was refluxed in acetonitrile for 48 hrs and concentrated to 30 mL. After addition of 50 mL of dichloromethane the resulting mixture was filtered through celite. Removal of the solvent under reduced pressure afforded a white gummy solid. Trituration in ether gave pure orthoester salt **6** as a white powder which was dried over P_2O_5 under vacuum (21.7 g, 87%): mp 196-197 ℃; ^{1}H NMR (DMSO-d_6) δ 0.85 (s, 3H), 1.83 (m, 2H), 3.59 (m, 2H), 3.84 (s, 6H), 7.75-7.92 (m, 15H); ^{13}C NMR (DMSO-d_6) δ 13.09, 16.24 (d, J=55.2), 29.96, 30.01, 72.23, 107.30 (d, J=15.5), 117.39 (d, J=82.2), 130.02, 134.20, 134.98; FAB MS, 419 (M-Br).

***N*-Cbz-5*S*-amino-6-phenyl-hex-3*Z*-enoic acid (8).** To a stirred solution of orthoester salt **6** (6.08 g, 12 mmol) in 60 mL of dry THF was added 2.19 g (11 mmol) potassium bis(trimethylsilyl)amide at −30 ℃ and the resulting mixture was stirred for 1 hr. The mixture was treated slowly with a solution of 3.0 g (10.6 mmol) of cbz-L-phenylalanal in 20 mL of THF (over 10 min.). The mixture was stirred for 1 hr at −30 ℃, for additional 1 hr at room temperature, then queched with water (10 mL). Concentration followed by flash column chromatography (using hexane : ethyl acetate : triethylamine, 80 : 18 : 2) afforded pure 5-L-(*N*-benzyloxycarbonyl) amino-6-phenyl-hex-3-*Z*-enyl-4'-methyl-2',6'-7'-trioxabicyclo-[2',2',2']-octane **7** as an oil.

A solution of **7** (2.5 g, 6 mmol) in *t*-butanol (60 mL), water (12 mL) and conc. HCl (7 mL) was refluxed for 10 hr. After removal of the solvent under reduced pressure the residue was dissolved in 5% aqueous K_2CO_3 solution and then washed three times with dichloromethane (30 mL×3). The aqueous layer was adjusted to pH 2, extracted with ethyl acetate (50 mL×2), and dried over anhydrous $MgSO_4$. Concentration of the organic layer afforded the target compound **8** in 91% yield (3.27 g) from cbz-L-phenylalanal: mp 90-91 ℃; $[\alpha]_D$=+30.6 (c=0.10, methanol); ^{1}H NMR (DMSO-d_6) δ 2.64 (m, 1H), 2.80 (m, 2H), 2.99 (m, 1H), 4.41 (m, 1H), 4.98 (s, 2H), 5.45 (dd, 1H), 5.52 (m, 1H), 7.14-7.39 (m, 10H), 7.49 (d, 1H), 12.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 33.09, 41.64, 50.15, 65.19, 122.72, 126.89, 127.97, 128.33, 128.89, 128.93, 129.81, 132.63, 137.42, 138.52, 155.34, 172.24; Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.76, H, 6.24, N, 4.13. Found: C, 70.65, H, 6.25, N, 4.15.

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Efficient Syntheses of 2-Acetyl-7-formylbenzofuran and 2-Acetyl-7-(formylmethyl)benzofuran through the Oxidative Cleavage of Allylbenzofuran with Osmium Tetraoxide/Sodium Periodate

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In connection with a program directed toward the synthesis of soft analogs of bufuralol,[1] we needed to synthesize 2-acetyl-7-formylbenzofuran (**1a**) as well as 2-acetyl-7-(formylmethyl)benzofuran (**1b**) as key intermediates. Since literature survey showed that there were no reports on the preparations of the desired intermediates, it is therefore important to develop efficient routes to two intermediates. In the several synthetic methods for benzofurans, cyclization reaction of substituted 2-hydroxybenzaldehydes with chloroacetone is used in the most common approach for the synthesis of the substituted 2-acetylbenzofurans as shown below.[2]