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New Approaches to the Asymmetric Synthesis of Dipeptide Isosteres *via β-Lactam Synthon Method*

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Abstract: New and efficient synthetic routes to dipeptide isosteres with high enantiomeric purity, e.g., hydroxyethylene, dihydroxyethylene and hydroxyethylamine isosteres, have been developed via oxiranes **6** and formyloxazolines **13** derived from *N*-t-Boc-β-lactams **4**.

It has been shown that hydroxyethylene, dihydroxyethylene and hydroxyethylamine dipeptide isosteres are essential building blocks[1] for the inhibitors of such enzymes as renin and HIV-1 protease.[2] These dipeptide isosteres provide effective transition state mimics of the substrates for the peptidases, which bind to the enzymes tightly and inhibit their actions.[3] Thus, a number of methods has been reported for the synthesis of these dipeptide isosteres.[4] In the course of our study on the exploration of the *"β-Lactam Synthon Method"* (β-LSM),[5] we have developed new and efficient methods for the syntheses of norstatine and its analogs[6] as well as norstatine-dipeptides and their analogs through novel ring-opening coupling of *N*-acyl-β-lactams,[7] which is applicable to resin-bound amino acids for solid phase peptide syntheses.[8] This type of ring-opening coupling of *N*-acyl-β-lactams has also been successfully applied to the efficient and practical syntheses of taxane antitumor agents[9] and novel hydroxy(keto)ethylene dipeptide isosteres.[10] We have further investigated the useful transformations of isoserines readily obtained by methanolysis of *N*-acyl-β-lactams and synthesized enantiopure 3-t-Boc-aminoalkene-1,2-oxides and 5-formyl-1,3-oxazolines. We communicate here new and efficient routes to hydroxyethylene, dihydroxyethylene and hydroxyethylamine dipeptide isosteres with high enantiomeric purity via these oxiranes and formyloxazolines derived from 1-t-Boc-3-siloxy-β-lactams.

Enantiopure (3*R*,4*S*)-1-(t-Boc)-3-siloxy-β-lactams **4b-d** were readily obtained through efficient chiral ester enolate-imine cyclocondensations, followed by removal of *p*-methoxyphenyl (PMP) and protection as carbamates in the same manner as reported previously from these laboratories. Due to the acidity of the benzylic protons of the aldimine, the corresponding 4-benzyl-β-lactam **4a** could not be obtained directly through the cyclocondensation route.[11-13] However, **4a** can be readily prepared from 4-isobutenyl β-lactam (Scheme 1). The ozonolysis of **1** gave, after reductive workup, the corresponding aldehyde which was subsequently treated with phenylmagnesium bromide. The resulting secondary alcohol was acetylated to give **2** in 66% overall yield. Although only one stereoisomer was obtained, the absolute stereochemical configuration of **2** has not been determined yet. Hydrogenolysis of **2** under 100 psi of hydrogen gave the desired 4-benzyl-β-lactam **3** in 74% yield. Removal of the PMP group of **3** [9] and protection as a carbamate gave **4a** in 87% overall yield.

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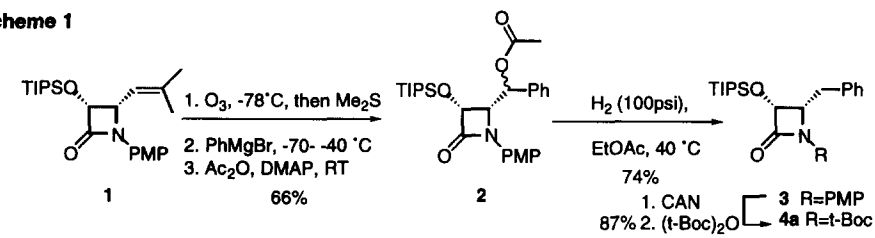
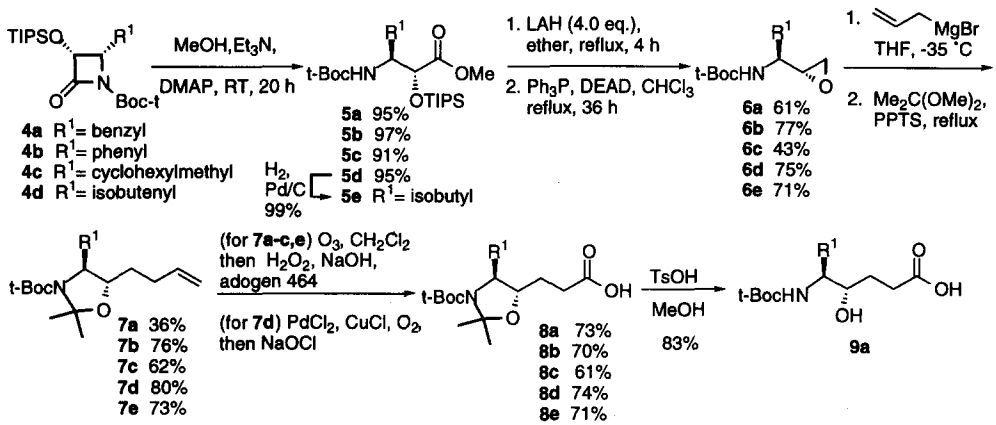
Scheme 1



As Scheme 2 shows, methanolysis of t-Boc-β-lactams **4a-d** gave *N*-t-Boc-O-TIPS-isoserine methyl esters **5a-d** in 91-97% yields. 4-Isobutenylisoserine **5d** was converted to the corresponding isobutylisoserine (norstatine) methyl ester **5e** by hydrogenation on Pd-C in 99% yield. In order to synthesize oxiranes **6**, **5a-e** were reacted with $LiAlH_4$ (LAH) and the resulting diols were subjected to the Mitsunobu reaction [14] to give oxiranes **6a-e** in 43-77% yields for two steps. Regioselective opening of oxiranes **6a-e** afforded the corresponding alcohols, which were then protected with 2,2-dimethoxypropane to give oxazolines **7a-e** in 36-80% yields for two steps. Ozonolysis of the alkene moieties of **7a-c** and **7e** gave, after oxidative workup, the *N,O*-protected hydroxyethylene isosteres **8a-c** and **8e** in 61-74% overall yields. Due to the presence of another olefin moiety in isobutenylisoserine **7d** which is susceptible to ozonolysis, an alternative procedure was employed, i.e., Wacker oxidation [15] followed by treatment with sodium hypochlorite, to give **8d** in 74% yield. Deprotection of **8a** with *p*-toluenesulfonic acid in MeOH gave *N*-t-Boc-hydroxyethylene isostere **9a** in 83% yield. Thus, other oxazolines **8b-e** should give the corresponding *N*-t-Boc-hydroxyethylene isostere **9b-e**.

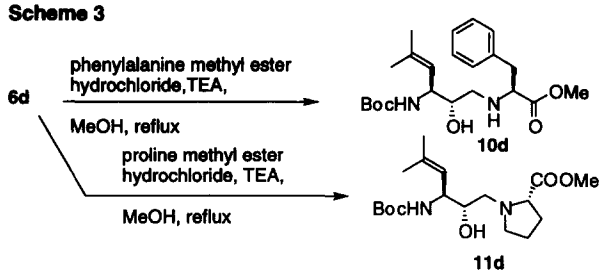
Scheme 2



Hydroxyethylamine isosteres can also be obtained from oxirane **6d**. Ring opening-coupling of **6d** with (*S*)-proline and (*S*)-phenylalanine methyl esters gave the corresponding hydroxyethylamine isosteres **10d** and **11d** in 76% and 74% yields, respectively (Scheme 3).

As Scheme 4 illustrates, the other useful intermediate, 5-formyl-1,3-oxazolines **13**, were also synthesized from **5a-e**. Removal of TIPS of **5a-e** followed by treatment with 2,2-dimethoxypropane / pyridinium *p*-toluenesulfonate (PPTS) gave oxazoline esters **12a-e** in 72-82% yields for two steps. Reduction of the ester moiety with diisobutylaluminum hydride (DIBALH) followed by Swern oxidation gave formyloxazolines **13a-e** in 78-87% overall yields.

Scheme 3



Lewis acid mediated allyllation of **13a-e** gave adducts **14a-e** with moderate to good *anti*- selectivities (Table 1). The absolute configuration of **14e** was determined by X-ray analysis (Figure 1). Ozonolysis of **14a-c** and **14e** followed by oxidative workup gave *N,O*-protected dihydroxyethylene isosteres **15a-c** and **15e** in 56-71% yields. Oxazoline **14d** (R^1 = isobutenyl) was subjected to Wacker oxidation followed by treatment with sodium hypochlorite to give **15d** in 53% yield. Deprotection of **15a** (R^1= $PhCH_2$) gave dihydroxyethylene isostere **16a** in 77% yield.

Scheme 4

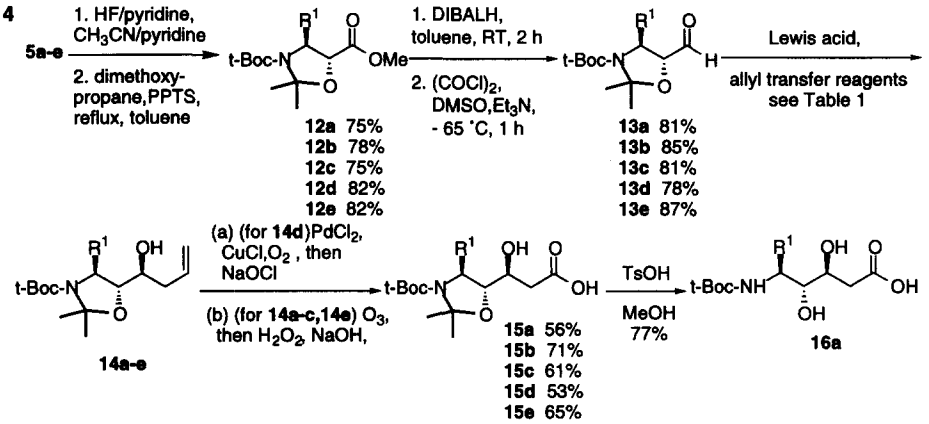
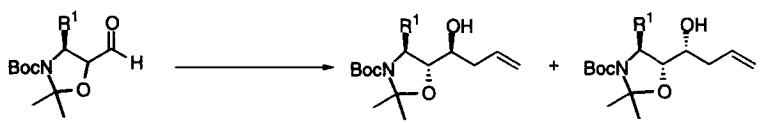
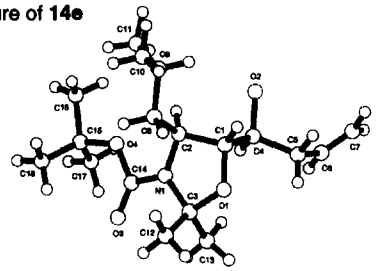


Table 1 Lewis acid mediated allyl addition to formyloxazolines 13



entry	R^1	Lewis acid	allylating reagent	solvent	yield (%)	*anti*: *syn*
1	isobutenyl	$TiCl_4$	allyltributyltin	CH_2Cl_2	50	2:3
2		$SnCl_4$	allyltributyltin		87	2:3
3[11]			allyltrichlorotin		55	8:1
4		$CrCl_2$	allyl bromide	THF	84	3:2
5	cyclohexylmethyl	$BF_3{\cdot}OEt_2$	allyltributyltin	CH_2Cl_2	75	7:1
6		$MgBr_2{\cdot}Et_2O$			71	3:1
7		$CrCl_2$	allyl bromide	THF	84	2.2:1
8	benzyl	$BF_3{\cdot}OEt_2$	allyltributyltin	CH_2Cl_2	70	6.5:1
9		$SnCl_4$			85	3:1

Figure 1 X-ray structure of **14e**



Further studies on the asymmetric synthesis of a variety of dipeptide isosteres via *N*-acyl-β-lactams **4**, oxiranes **6**, formyloxazolines **13** and their applications to the synthesis of enzyme inhibitors are actively underway.

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