68.0, 67.3, 67.2, 63.2, 59.0.
17. **10:** IR (neat, cm^{-1}) 3300 (alkyne), ^1H NMR δ (400 MHz, $CDCl_3$) 5.80 (ddd, 1H, J_1=6.9 Hz, J_2=10.5 Hz, J_3= 17.4 Hz, 2-H), 5.30 (m, 2H, 1-H2), 4.80 (m, 6H, 2x (OCH^2O) (MEM)), 4.23 (m, 1H, 4-H), 3.4-4.0 (m, 14H, 3x(OCH_2CH_2O) (MEM) and 3-H and 5-H), 3.36 (s, 9H, 3xOCH_3 (MEM)), 2.60 (m, 2H, 6-H_2), 1.95 (t, 1H, J=2.6 Hz, 8-H); MS (FAB) 315 (M^+-1, 100%).
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19. **12:** $[\alpha]_D^{25}$ = – 92.5°(c=0.62, $CHCl_3$); UV λ_{max} (EtOH) 265 nm; ^1H NMR δ (400 MHz, $CDCl_3$) 6.36 (d, 1H, J= 11.2 Hz, 6-H), 6.02 (d, 1H, J=11.2 Hz, 7-H), 5.42 (m, 1H, 19-H), 5.08 (m, 1H, 19-H), 4.22 (m, 1H, 1-H), 4.15 (m, 1H, 3-H), 3.50 (m, 1H, 2-H), 3.04 (s, 1H, OH), 2.80 (dd, J_1=12.0 Hz, J_2=3.8 Hz, 1H, 9-H), 2.58 (S, 1H, OH), 2.48 (m, 2H, 4-H_2), 2.24 (s, 1H, OH), 0.91 (d, 3H, J= 6.3 Hz, 21-CH_3), 0.87 (d, J=1.7 Hz, 3H, 26-CH_3), 0.85 (d, J=1.7Hz, 3H, 27-CH_3), 0.54 (s, 3H, 18-CH_3).

Efficient Synthesis of Hydroxyethylidene and *(E)*- Alkene Dipeptide Isosteres

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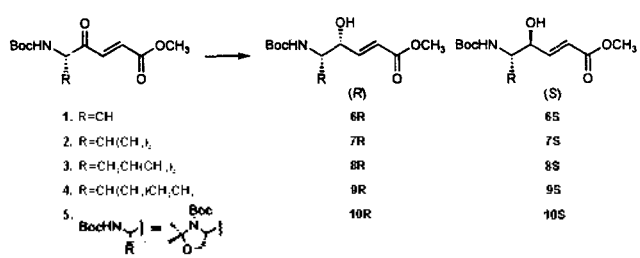
The development of novel dipeptide isosteres possesses a great value and importance in peptidomimetics. Among more than dozen peptide isosteres,[1] *(E)* -alkene dipeptide isostere[2] is a suitable amide bond surrogate in terms of mimicking the rigidity, bond angles, and bond length of the amide bond. We wish to report here general and efficient synthesis of hydroxyethylidene[3] and *(E)* -alkene dipeptide isosteres, which would considerably increase their application to drug and development.

Hydroxyethylidene dipeptide isostere first reported by Hanson *et al.* [3a] is an interesting dipeptide analog which combines conformational restriction, function as statine mimics, and the ability to undergo conjugate addition to enzyme nucleophiles such as cysteine thiol. Previous syntheses[3b,c,d] of hydroxyethylidene dipeptide isosteres mainly resorted to the Hansons method,[3a] which was hampered by the lack of Stereoselectivity in the vinylmagnesium halide addition to amino aldehydes, long reaction steps, and low overall yields. As a solution to the synthetic problem in preparing hydroxyethylidene dipeptide isosteres, we have developed an efficient route from ketovinyl dipeptide isostere.[4] Reduction of ketovinyl dipeptide isostere gives the corresponding hydroxyethylidene dipeptide isostere in one step (Scheme 1).

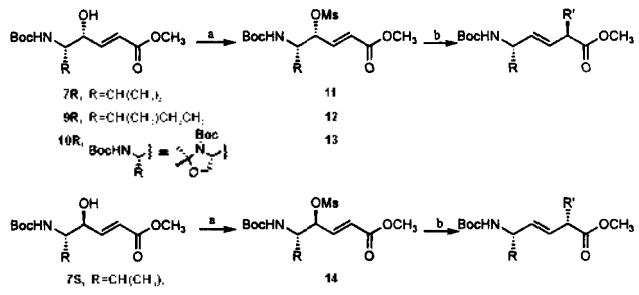
Various reducing agents including $NaBH_4$, $Zn(BH_4)_2$, LiBEt$_3$H, L-selectride, LS-selectride, LiAl(*i*- Bu)$_2$(*n*- Bu)$_2$, and $NaBH_3CN$ were used and additives such as Et_3BOMe, $ZnCl_2$, $CeCl_3$, and $SmCl_3$ were employed. Even though the Stereoselectivity of reduction was moderate (product ratio, *(R)* : *(S)* =88 : 12-18 : 82),[5] combined isolated yields of *(R)*- and *(S)*- alcohols were good to excellent (55-99%). Furthermore, by employing some additives ($CeCl_3$, $SmCl_3$) diastereoselectivity could be reversed and both diastereomers of hydroxyethyliene dipeptide isosteres could be prepared. Due to ease access of ketovinyl dipeptide isosteres from amino acids,[4] this synthetic route constitutes an efficient and general pathway for hydroxyethyliene dipeptide isosteres. Conversion of hydroxyethylidene to *(E)*- alkene dipeptide isosteres through γ-mesyloxy *(E)*- α,β-enoate intermediates was completed by using Ibuka's method.[3b]

Anti-S_N2' displacement of γ-mesyloxy leaving group with orgnocopper. BF_3 complex provided *(E)*- alkene dipeptide isostere in a stereoselective manner (Scheme 2). Experimental results are summarized in Table 1.

The salient features of this synthetic route for *(E)*- alkene dipeptide isosteres include: (1) the relatively few number of steps required, (2) excellent chemical yields and Stereoselectivity. Due to the simplicity and efficiency in preparation of scalemic γ-hydroxy α,β-enoates(hydroxyethylidene) and a

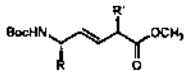
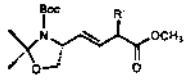
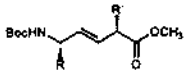


Scheme 1.



Scheme 2. Reagents and conditions: (a) MsCl, pyridine, CH_2Cl_2, 0 °C. (b) CuCN, R'MgCl, BF_3-Et_2O, THF, – 78 °C.

Table 1. Synthesis of *(E)*- alkene dipeptide isosteres

substrate	*(E)*- alkene dipeptide isostere	yield	diastereo-Selectivity (R) : (S)[a]	$[\alpha]_D$ (c, $CHCl_3$)
11				
	R=CH(CH$_3$)$_2$			
	R'=CH(CH$_3$)$_2$	89	99:1	−35.9(0.88)
	R'=CH$_2$CH(CH$_3$)$_2$	88	99:1	−40.3(0.88)
	R'=C(CH$_3$)$_3$	55[c]	95:5	−26.5(0.92)
12	R=CH(CH$_3$)CH$_2$CH$_3$			
	R'=CH$_3$	69[d]	86:14	−22.2(0.94)
	R'=CH(CH$_3$)$_2$	89	99:1	−29.5(0.87)
	R'=CH$_2$CH(CH$_3$)$_2$	85	99:1	−42.4(1.02)
	R'=C(CH$_3$)$_3$	74[e]	99:1	−2.3(1.07)
13				
	R'=CH(CH$_3$)$_2$	95	99:1	−56.2(1.42)
	R'=CH$_2$CH(CH$_3$)$_2$	93	99:1	−41.2(1.07)
	R'=C(CH$_3$)$_3$	93	99:1	−58.6(0.57)
14				
	R=CH(CH$_3$)$_2$			
	R'=CH$_3$	83[f]	1:99	+18.9(1.31)
	R'=CH(CH$_3$)$_2$	92	1:99	+17.8(1.60)
	R'=CH$_2$CH(CH$_3$)$_2$	91	1:99	+26.5(1.09)
	R'=C(CH$_3$)$_3$	73[g]	2:98	+8.02(1.09)
15	R=CH(CH$_3$)CH$_2$CH$_3$			
	R'=CH$_3$	84	1:99	+30.7(1.18)
	R'=CH(CH$_3$)$_2$	80	5:95	+37.7(1.13)
	R'=CH$_2$CH(CH$_3$)$_2$	93	1:99	+43.1(0.98)
	R'=C(CH$_3$)$_3$	88[h]	1:99	+20.0(1.01)

[a]Isolated yield of the major product. Configuration at C2 center. [b]Obtained along with 11% reductive elimination product. [c]Obtained along with 14% reductive elimination product. [d]Obtained along with 11% reductive elimination product. [e]Obtained along with 6% reductive elimination product. [f]Obtained along with 15% reductive elimination product. [g]Obtained along with 10% reductive elimination product.

variety of available organocopper reagents, this synthetic route for *(E)*- alkene dipeptide isosteres is a valuable addition to the arsenal of reliable synthetic pathways and will be often applied to peptidomimetics.

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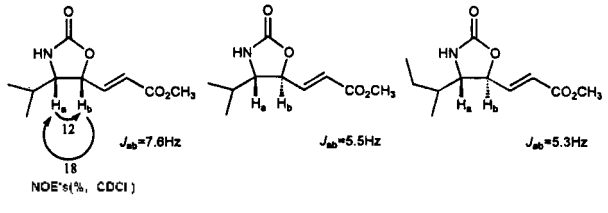
5. The absolute configuration of **6R** and **6S** compounds was determined by the comparison of ^{1}H NMR chemical shift values of those compounds with the literature[3b] values of compound **6S.** In the case of compounds **7R, 7S,** and **9R** corresponding oxazolidone derivatives were prepared and the absolute configuration was determined by the comparison of coupling constants (J_{ab}) with the literature values and the NOE experiment.



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