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Ketovinyl Dipeptide Isosteres: A General Synthesis and Conformational Study

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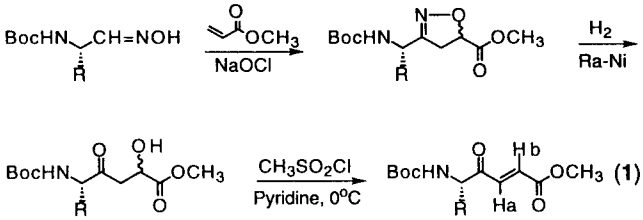
Dipeptide isosteres have been well utilized in the synthesis of pharmacologically important enzyme inhibitors. Ketovinyl dipeptide isostere[1] is an interesting dipeptide analog which combines conformational restriction and the ability to undergo conjugate addition upon reaction with nucleophilic species from the respective receptor or enzyme binding sites. In 1985, this isostere was firstly introduced by Hanson and Lindberg[1a] with only one example (Boc-L-Phe-Ψ[COCH=]-Gly-L-Pro-OMe) and very recently Italian chemists[1b] have reported two examples (Boc-L-Val-Ψ[COCH=]-Gly-OEt, Boc-L-Phe-Ψ[COCH=]-Gly-OEt) of ketovinyl dipeptide isostere. However both groups could synthesize the ketovinyl isosteres of limited scope. We have been interested in the development of an efficient and general synthesis of ketovinyl dipeptide isostere. Here, we wish to report a facile synthesis of ketovinyl dipeptide isosteres and conformational analysis results aided with *ab initio* calculations.

Results and Discussion

Ketovinyl dipeptide isosteres were prepared from the corresponding α-amino aldoximes in a three step sequence; (1) 1,3-dipolar cycloaddition with methyl acrylate, (2) reductive cleavage[2] of Δ^2-isoxazoline, and (3) dehydration reaction to the final product (Eq. 1). The synthesis of starting materials, α-amino aldoximes from α-amino acids has already been reported from this laboratory.[3] α-Amino nitrile oxides which were generated *in situ* from the reaction of the corresponding α-amino aldoximes and sodium hypochlorite underwent dipolar cycloadditions with methyl acrylate smoothly to give a diastereomeric mixture of cycloadducts. These cycloadducts were directly subjected under the reductive cleavage conditions [Ra-Ni, H_2(1 atm), $B(OH)_3$, MeOH : H_2O=5 : 1] and a diastereomeric mixture of α-hydroxy ketomethylene isosteres were produced. Dehydration of α-hydroxy ketomethylene isosteres using the Kozikowski conditions[4] afforded *E*-olefinic ketovinyl dipeptide isosteres in good yields. The olefinic geometry was readily assigned as *E* from the inspection of coupling constants between Ha and Hb protons (Ja, b=15.5-16.2 Hz).



(1)

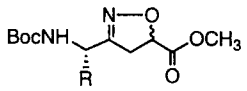
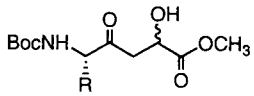
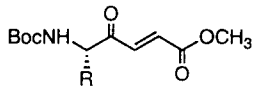
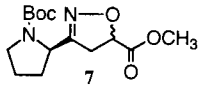
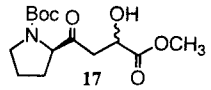
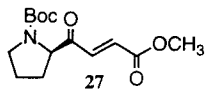
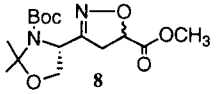
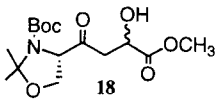
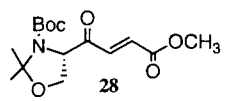
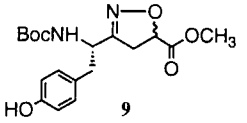
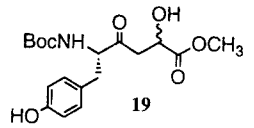
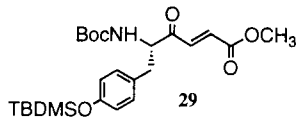
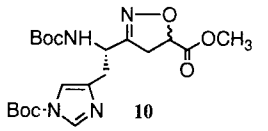
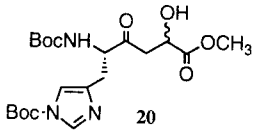
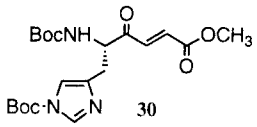
The experimental results are summarized in Table 1. From nine natural and one unnatural (cyclohexylalanine, Cha) amino acids, ten different ketovinyl dipeptides were synthesized efficiently using the three step sequence. Reaction yields in all the steps were very high (mostly, more than 80%). It is noteworthy that *E*-olefinic ketovinyl dipeptide isosteres were formed as major products from diastereomeric mixtures of α-hydroxy ketomethylene dipeptide isosteres. These experimental results can be rationalized by the thermodynamic control of dehydration process under the Kozikowski conditions.[4] Therefore we can employ achiral dipolarophile such as methyl acrylate for the synthesis of ketovinyl dipeptide isosteres and it makes our procedure more efficient and practical.

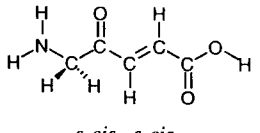
In order to investigate conformational preference of ketovinyl dipeptide isosteres, *ab initio* calculations of a model system (Gly-Ψ[COCH=]Gly) were carried out. Figure 1 shows four planar conformations and their relative energies at HF/6-31G** and MP2/6-31G** levels. The *s-cis, s-cis* conformer is calculated to be the most stable one and this conformational analysis suggests the utility of ketovinyl dipeptide isostere as a new building block for β-sheet structures.[5]

Experimental section

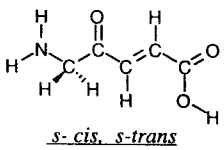
General Procedure. All commercial chemicals were used as obtained without further purification. Anhydrous solvents were obtained as follows: tetrahydrofuran, distillation from sodium/benzophenone; methylene chloride, toluene, dimethylformamide and pyridine, distillation from CaH_2. Mel-

Table 1. Synthesis of Ketovinyl Dipeptide Isosteres

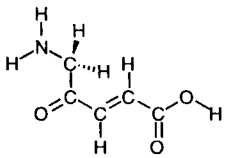
α-amino acid	2-isoxazoline isostere	yield (%)	α-OH ketomethylene isostere	yield (%)	ketovinyl isostere	yield (%)
						
(Ala)	**1** R=CH_3	65	**11** R=CH_3	92	**21** R=CH_3	85
(Val)	**2** R=$CH(CH_3)_2$	88	**12** R=$CH(CH_3)_2$	91	**22** R=$CH(CH_3)_2$	90
(Leu)	**3** R=$CH_2CH(CH_3)_2$	97	**13** R=$CH_2CH(CH_3)_2$	92	**23** R=$CH_2CH(CH_3)_2$	83
(Ile)	**4** R=$CH(CH_3)CH_2CH_3$	88	**14** R=$CH(CH_3)CH_2CH_3$	96	**24** R=$CH(CH_3)CH_2CH_3$	86
(Phe)	**5** R=CH_2Ph	98	**15** R=CH_2Ph	94	**25** R=CH_2Ph	94
(Cha)	**6** R=$CH_2C_6H_{11}$	99	**16** R=$CH_2C_6H_{11}$	82	**26** R=$CH_2C_6H_{11}$	91
(Pro)	 **7**	92	 **17**	93	 **27**	69
(Ser)	 **8**	96	 **18**	94	 **28**	91
(Tyr)	 **9**	71	 **19**	81	 **29**	56
(His)	 **10**	93	 **20**	62	 **30**	86



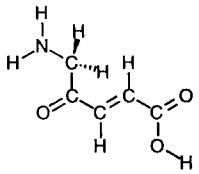
s-cis, s-cis
HF : 0.00 Kcal/mol
MP2 : 0.00 Kcal/mol



s-cis, s-trans
HF : 0.72Kcal/mol
MP2 : 0.74 Kcal/mol



s-trans, s-cis
HF : 2.71 Kcal/mol
MP2 : 1.20 Kcal/mol



s-trans, s-trans
HF : 2.96 Kcal/mol
MP2 : 1.77 Kcal/mol

Figure 1. Four planar conformers and their relative energies of Gly-Ψ[COCH=]-Gly.

ting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer using tetramethylsilane as internal standard. Infrared (IR) spectra were obtained on a BOMEM model FT-IR M100-C15 spectrometer as neat. Mass spectra (EI or FAB) were recorded on a KRATOS MS 25 RFA system. High resolution MS were performed by the Inter-University Basic-research Center, Seoul, Korea. Elemental analyses were performed by Galbraith Laboratories, Knoxville, USA. Optical rotations were recorded on a JASCO DIP-360 polarimeter or Rudolph Autopol III polarimeter. Column chromatography was performed with E. Merck 240-400 mesh silica gel. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates and visualized with UV light and/or 20% solution of phosphomolybdic acid in EtOH.

Preparation of Methyl (5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-4-oxo-2-hexenoate (21). To a precooled (0 ℃) solution of α-hydroxy ketomethylene isostere **11** (0.70 g, 2.5 mmol) in pyridine (50 mL) was added methanesulfonyl chloride (0.39 mL, 5.0 mmol). After 5 hours at 0 ℃, the reaction mixture was diluted with ethyl ether (100 mL) and washed with water and 1 N HCl (twice). The organic layer was dried over $MgSO_4$ and then concentrated. The product **21** (white solid, crude yield 85%) was purified by flash chromatography followed by recrystallization from ethyl ether/pentane (1/3). Rf=0.24 (Hex : EA=5 : 1); IR ($CHCl_3$, cm^{-1}) 3357, 2970, 1710, 1510, 1258, 1022; ^1H NMR ($CDCl_3$) δ 7.23 (d, J=16.0 Hz, 1H), 6.83 (d, J=15.8 Hz, 1H), 5.22 (br, 1H), 4.56 (br, 1H), 3.88 (s, 3H), 1.50 (s, 9H), 1.36 (d, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.6, 166.2, 155.7, 136.7, 132.6, 80.8,

55.2, 53.0, 28.9, 18.1; MS (m/e) 258 ($M^+ + 1$), 184, 170, 158, 144, 114, 88; mp 70-71 ℃; $[\alpha]_D^{24} = +2.0$ (c 3.79, $CHCl_3$); Anal. Calcd. for $C_{12}H_{19}O_5N$: C, 56.02; H, 7.44; N, 5.44 Found: C, 55.52; H, 7.54; N, 5.19.

Methyl (5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-6-methyl-4-oxo-2-heptenoate (22). (white solid, yield 90 %) Rf=0.48 (Hex : EA=3 : 1); IR ($CHCl_3$, cm^{-1}) 3327, 2966, 1732, 1684, 1532, 1366, 1173; ^1H NMR ($CDCl_3$) δ 7.22 (d, J=15.5 Hz, 1H), 6.80 (d, J=15.6 Hz, 1H), 5.13 (br, 1H), 4.52 (br, 1H), 3.82 (s, 3H), 2.17 (br, 1H), 1.44 (s, 9H), 1.02 (d, J=6.2 Hz, 3H), 0.80 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.9, 166.3, 156.5, 137.7, 132.2, 80.7, 64.1, 53.1, 30.8, 28.9, 20.4, 17.4; mp 62.5-63.5 ℃; $[\alpha]_D^{24} = +25.4$ (c 2.07, $CHCl_3$); Anal. Calcd. for $C_{14}H_{23}O_5N$: C, 58.93; H, 8.12; N, 4.91 Found: C, 58.94; H, 8.12; N, 4.82.

Methyl (5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-7-methyl-4-oxo-2-octenoate (23). (clear oil, yield 83%) Rf=0.27 (Hex : EA=6 : 1); IR ($CHCl_3$, cm^{-1}) 3337, 2959, 1711, 1509, 1368, 1159; ^1H NMR ($CDCl_3$) δ 7.19 (d, J=15.8Hz, 1H), 6.78 (d, J=15.8 Hz, 1H), 5.00 (d, J=7.5 Hz, 1H), 4.52 (br, 1H), 3.78 (s, 3H), 1.73-1.49 (m, 3H), 1.40 (s, 9H), 0.95 (d, J=6.5 Hz, 3H), 0.90 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.2, 166.3, 156.2, 137.2, 132.3, 80.7, 58.0, 53.2, 53.0, 41.1, 28.9, 25.5, 23.8, 22.4; MS (m/e) 300 ($M^+ + 1$), 244, 200, 186, 142, 112, 99; $[\alpha]_D^{24} = +6.3$ (c 1.12, $CHCl_3$).

Methyl (5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-6-methyl-4-oxo-2-octenoate (24). (yellow solid, yield 86 %) Rf=0.66 (Hex : EA=2 : 1); IR ($CHCl_3$, cm^{-1}) 3362, 2970, 1709, 1509, 1367, 1008; ^1H NMR ($CDCl_3$) δ 7.23 (d, J=15.9 Hz, 1H), 6.79 (d, J=15.8 Hz, 1H), 5.15 (br, 1H), 4.52 (br, 1H), 3.82 (s, 3H), 1.90 (br, 1H), 1.44 (s, 9H), 1.31 (m, 1H), 1.18 (m, 1H), 0.99 (d, J=6.2 Hz, 3H), 0.88 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.1, 166.3, 156.3, 137.7, 132.0, 80.6, 63.9, 53.0, 37.6, 28.9, 24.9, 16.7, 12.2; MS (m/e) 300 ($M^+ + 1$), 244, 226, 200, 186, 142, 130, 99; mp 42.5-43.5 ℃; $[\alpha]_D^{28} = +53.4$ (c 1.46, $CHCl_3$).

Methyl (5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-4-oxo-6-phenyl-2-hexenoate (25). (white needle, yield 94 %). Rf=0.31 (Hex : EA=5 : 1); IR ($CHCl_3$, cm^{-1}) 3364, 2967, 1707, 1505, 1392, 1169; ^1H NMR ($CDCl_3$) δ 7.27-7.06 (m, 5H), 7.16 (d, J=15.9 Hz, 1H), 6.75 (d, J=15.8 Hz, 1H), 5.11 (br d, J=7.0 Hz, 1H), 4.75 (dd, J=13.5, 6.6 Hz, 1H), 3.79 (s, 3H), 3.14 (dd, J=13.9, 6.2 Hz, 1H), 2.98 (dd, J=13.9, 6.3 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 197.2, 165.5, 136.5, 135.5, 131.7, 129.3, 128.6, 127.1, 59.7, 52.3, 37.4, 28.2; MS (m/e) 333 (M^+), 314, 231, 148, 110, 83, 69, 57; mp 98-99.5 ℃; $[\alpha]_D^{24} = +21.8$ (c 1.00, $CHCl_3$); Anal. Calcd. for $C_{18}H_{23}O_5N$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.53; H, 6.87; N, 4.15.

Methyl (5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-6-cyclohexyl-4-oxo-2-hexenoate (26). (clear oil, yield 91 %) Rf=0.55 (Hex : EA=3 : 1); IR ($CHCl_3$, cm^{-1}) 3357, 2924, 1709, 1510, 1366, 1283, 1170; ^1H NMR ($CDCl_3$) δ 7.15 (d, J=15.8 Hz, 1H), 6.75 (d, J=15.6 Hz, 1H), 5.03 (d, J=7.4 Hz, 1H), 4.54 (br, 1H), 3.76 (s, 3H), 1.82 (br, 1H), 1.68-1.59 (br m, 5H), 1.43-1.25 (br m, 10H), 1.24-1.06 (m, 4H), 0.91-0.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 198.6, 165.6, 155.4, 136.5, 131.5, 79.9, 56.6, 52.2, 38.9, 34.1, 33.8, 32.4, 28.2, 26.2, 26.1, 25.9; MS (m/e) 340 ($M^+ + 1$), 284, 240, 170, 126, 99, 82; $[\alpha]_D^{24} = +24.6$ (c 1.00, $CHCl_3$).

Methyl (2′*S*,2*E*)-4-[*N*-(*tert*-butyloxycarbonyl)pyrrolidin-2′-yl)-4-oxo-2-butenoate (27). (white solid, yield 69 %) Rf=0.29 (Hex : EA=3 : 1); IR ($CHCl_3$, cm^{-1}) 2972, 1707, 1395, 1286, 1167; ^1H NMR ($CDCl_3$) δ 7.19(d, J=15.8 Hz, 1H), 6.77 (d, J=15.7 Hz, 1H), 4.54-4.35 (m, 1H), 3.76 (s, 3H), 3.58-3.45 (m, 2H), 2.18 (m, 1H), 1.92-1.77 (m, 3H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 198.2, 165.6, 153.7, 135.5, 131.6, 80.6, 64.9, 52.3, 46.7, 29.8, 28.8, 23.7; MS (m/e) 284 ($M^+ + 1$), 228, 184, 170, 114, 96, 82; mp 77-78 ℃; $[\alpha]_D^{24} = -61.3$ (c 1.07, $CHCl_3$); Anal. Calcd. for $C_{14}H_{21}O_5N$: C, 59.35; H, 7.47; N, 4.94 Found: C, 59.21; H, 7.48; N, 4.90.

Methyl (4′*S*,2*E*)-4-[3′-*N*-(*tert*-butyloxycarbonyl)-2,2-dimethyloxazolidin-4′-yl]-4-oxo-2-butenoate (28). (white solid, yield 91%) Rf=0.63 (Hex : EA=1 : 1); IR ($CHCl_3$, cm^{-1}) 2973, 1706, 1393, 1367, 1269, 11174; ^1H NMR ($CDCl_3$) δ 7.28 (d, J=16.2 Hz, 1H), 6.78 (d, J=16.2 Hz, 1H), 4.64-4.52 (br, 1H), 4.17 (t, J=8.4 Hz, 1H), 3.96 (br d, 1H), 3.80 (s, 3H), 1.69 (br s, 3H), 1.54 (s, 3H), 1.42-1.27 (br d, 9H); ^{13}C NMR ($CDCl_3$) δ 166.2, 136.1, 132.5, 81.8, 65.4, 53.0, 28.9, 26.1, 24.6; MS (m/e) 314 ($M^+ + 1$), 258, 240, 214, 200, 182, 156, 100, 84, 72; mp 90.5-91.5 ℃; $[\alpha]_D^{21} = -78.1$ (c 1.03, $CHCl_3$); Anal. Calcd. for $C_{15}H_{23}O_6N$: C, 57.50; H, 7.40; N, 4.47 Found: C, 57.49; H, 7.65; N, 4.18.

Methyl(5*S*)-5-(*tert*-butyloxycarbonyl)amino-6-(4-*O*-*tert*-butyldimethylsilyl)oxyphenyl-4-oxo-2-hexenoate (29). (clear oil, yield 56%); Rf=0.64(Hex : EA=3 : 1); IR (neat, cm^{-1}) 2947, 1712, 1509, 1258 1159; ^1H NMR ($CDCl_3$) δ 7.34 (br, 1H), 7.14 (m, 1H), 6.96 (d, J=8.1 Hz, 1H), 6.75 (m, 3H), 5.11 (br, 1H), 4.72 (br, 1H), 3.79 (s, 3H), 3.04-2.93 (m, 2H), 1.47 (s, 3H), 1.41 (s, 3H), 0.97 (s, 9H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 198.2, 172.8, 166.2, 155.3, 150.8, 137.2, 132.2 131.2, 130.9, 128.7, 127.1, 120.8, 83.2, 60.4, 52.9, 42.6, 37.3, 28.9, 28.6, 26.3, 18.8, −3.7; MS (m/e) 464 ($M^+ + 1$), 309, 250, 221, 163, 135, 99, 75; $[\alpha]_D^{24} = +1.5$ (c 2.31, $CHCl_3$).

Methyl(5*S*,2*E*)-5-(*tert*-butyloxycarbonyl)amino-6-(N^{im}-(*tert*-butyloxycarbonyl)imidazoyl-4-oxo-2-hexenoate (30). (clear oil, yield 86%); Rf=0.57 (Hex : EA=1 : 2); IR ($CHCl_3$, cm^{-1}) 3365, 2970, 1712, 1497, 1391, 1287, 1162; ^1H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.31 (d, J=16.2 Hz, 1H), 7.13 (s, 1H), 6.78 (d, J=16.2 Hz, 1H), 5.89 (br, 1H), 4.71 (m, 1H), 3.80 (s, 3H), 3.05 (br, 2H), 1.61 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 198.3, 166.3, 156.1, 147.4, 138.7, 137.5, 136.9, 132.0, 115.4, 86.3, 80.7, 59.1, 52.9, 29.8, 28.8, 28.4; MS (m/e) 424 ($M^+ + 1$), 368, 310, 270, 198, 154, 111, 97, 82; $[\alpha]_D^{23} = -1.0$ (c 1.07, $CHCl_3$).

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Error	Correction
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