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HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF (6-METHYLENEPYRROLO[1,2-*C*]OXAZOL-7-YL)-METHYLPHOSPHONATE BY AN APPLICATION OF RADICAL REACTION

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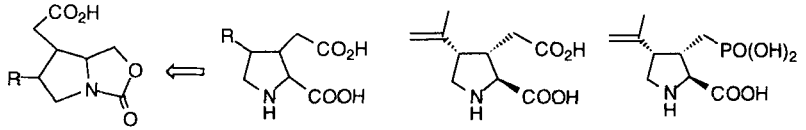
Abstract : Highly diastereoselective synthesis of (6-methylenepyrrolo[1,2-*c*]-oxazol-7-yl)methylphosphonate **5** was achieved by an application of intramolecular radical cyclization of vinyl radical to β-carbon of unsaturated phosphonate.

The development of new methodologies for the stereocontrolled construction of 6,7-disubstituted pyrroloxazolidinones **1**[1] is of particular relevance to 3,4-disubstituted pyrrolidine-2-carboxylic acids **2**,[2] which provide definitive structural feature of kainoids **3** and related compounds.[3] Phosphono kainoids such as **4**, obtained by replacement of ω-carboxyl acid with a phosphonyl acid group, have been known to show potent antagonistic activity to the kainic acid receptor.[4]



1 R=aliphatic, aromatic **2** **3** **4**

It is important, from the point of view of medicinal chemistry, to get the versatile intermediates to give compounds showing antagonistic activity to

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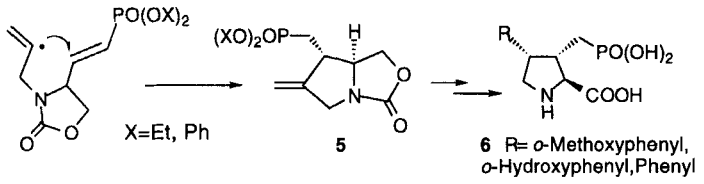
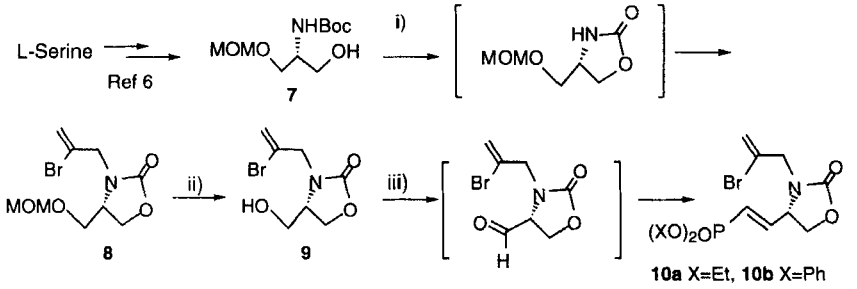
excitatory amino acids receptors. We examined the facile synthesis of the (6-methylenepyrrolo[1,2-*c*]oxazol-7-yl)methylphosphonate **5**, versatile intermediate for the preparation of 4-substituted 3-phosphonomethylproline **6**. The route chosen to (6-methylenepyrrolo[1,2-c]oxazol-7-yl)methylphosphonate **5** featured a radical mediated cyclization using α,β-unsaturated phosphonate as a radical acceptor (Scheme 1).[5] The reaction was found to proceed with high diastereoselectivity. We wish to disclose the results of our studies.

Scheme 1



The radical precursors, *N*-substituted oxazolidinones **10a,b** which contain a latent radical center, were synthesized from the (*2R*)-2-[(*tert*-butoxycarbonyl)-amino]-3-(methoxymethoxy)propan-1-ol **7**[6] as outlined in the Scheme 2 by starting with L-Serine. Ring closure of **7** by treatment with NaH followed by bromoallylation of the oxazolidinone, formed in situ, with 2,3-dibromopropene in one-pot manner yielded 3-bromoallyl-4-[(methoxymethoxy)methyl]oxazolidinone **8**. Removal of methoxymethoxy group of **8** was effectively achieved by treatment with Amberlist in methanol to afford alcohol **9**. Swern oxidation of **9**, followed by

Scheme 2



Reagent and Conditions

i) NaH, 2,3-dibromopropene/THF ii) Amberlist/MeOH iii) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2 then $Ph_2P{=}CHP(O)(OEt)_2/CH_2Cl_2$ or $Ph_3P{=}CHP(O)(OPh)_2/CH_2Cl_2$

Wittig phosphonylation of the resulting aldehyde with [(diethylphosphinyl)methylidene]triphenylphosphorane[7], [(Ph_3P)=CHP(O)($OEt)_2$], and [(Diphenoxyphosphinyl)methylidene]triphenylphosphorane[7], [(Ph_3P)=CHP(O)($OPh)_2$], gave **10a,b** in 43, 38% yield respectively. The β-carbon of vinylphosphonate of **10a,b** can be considered as an efficient radical acceptor because of the presence of electron withdrawing phosphonyl substituent.[5] Radical cyclization of **10a,b** thus obtained was examined. Heat of a benzene solution of **10a** with 1.5 equiv. of Bu_3SnH in the presence of AIBN gave (7*S*,7a*S*)-**11a** as a single product in 69% yield. The reaction was surprisingly found to proceed with high diastereoselectivity and the formation of (7*R*,7a*S*)-isomer was not observed. The *trans*-selective exo-trig-cyclization can be accounted for by taking the thermodynamically more stable transition state **A** rather than **B** which was considerably unfavorable owing to 1,3-allylic strain as depicted in Figure 1. The yield of **11a** was raised to 83 % when the reaction was carried out at 0°C in toluene solution (2 mM) by using Et_3B as a radical initiator instead of AIBN. In a next stage, **10b** of which phosphonic ester substituent is more bulky than that of **10a**, was reacted with Bu_3SnH in benzene solution at 80°C in the presence of AIBN (entry 2) yielded (7*S*,7a*S*)-**11b** as a sole product in 68% yield. Conduction of the reaction by the use of Et_3B instead of AIBN at low temperature (0°C) improved the yield of **11b** (entry 4, 78% yield). The behavior of the radical reaction of **10b**, gave the similar results to that of **10a** in yield of the corresponding cyclization product and diastereoselectivity.

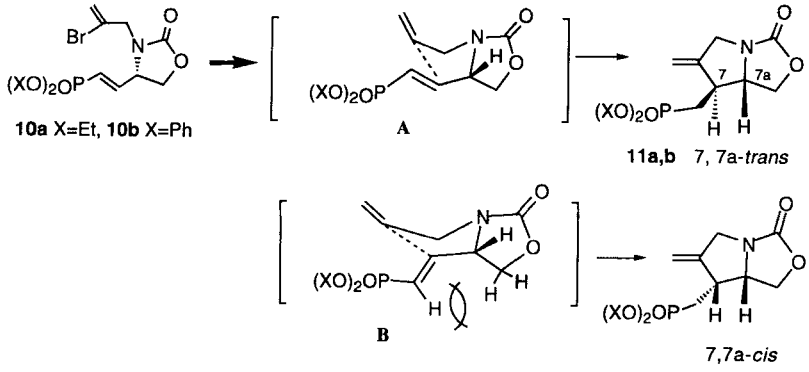


Figure 1

Table 1 Radical cyclization of 10a,b

Entry	X	Reaction Conditin	Yield (7,7a-*trans*)
1	Et	Bu_3SnH / AIBN / benzen, 80°C / 3hr	69
2	Ph	Bu_3SnH / AIBN / benzen, 80°C / 3hr	68
3	Et	Bu_3SnH /Et_3B / toluene, 0°C / 12hr	83
4	Ph	Bu_3SnH / Et_3B / toluene, 0°C / 12hr	78

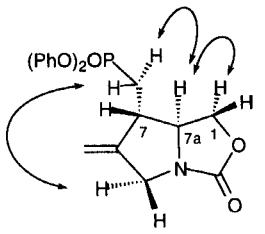


Figure 2 NOESY Correlation of **11b**

The stereochemistry of the cyclization products was determined by ^1H, ^{13}C-NMR and NOESY (Figure 2) experiments of **11b**. All of the proton and carbon signals of the cyclization products **11a,b** could be assigned satisfactorily.

The radical cyclization was found to proceed with highly diastereoselectivity to give (6-methylenepyrrolo[1,2-*c*]oxazol-7-yl)methylphosphonates **11a,b** potentially useful intermediates for a synthesis of a variety of 4-substituted 3-phosphorylmethylpyrrolidine-2-carboxylic acids.

Experimental

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under nitrogen. Tetrahydrofuran (THF) and ether were distilled from Na/benzophenone, methylene chloride (CH_2Cl_2) was distilled from CaH_2. Column chromatography was performed on silica gel 60 (0.043-0.063mm) was used and the columns were eluted in the flash mode. ^1H NMR spectra were recorded on a Bruker AM 400 or Varian Gemini 300 spectrometer operating at 400 MHz and 300MHz, respectively, for solution in $CDCl_3$. The chemical shifts, relative to

tetramethylsilane (TMS) where δ (TMS)=0, and coupling constants (*J*) are give as δ values (ppm) and in Hz respectively. The multiplicity of the signal is indicated as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, br=broad signal. ^{13}C NMR spectra were recorded in $CDCl_3$ on the Bruker AM-400 (100 MHz). Chemical shifts are recorded relative to $CDCl_3$ (central line of triplet, δc 77.0) unless otherwise stated. IR spectra were recorded by using Perkin-Elmer FT-IR 1710 spectrometer. Mass spectra (MS) were measured on a TSQ 700 and VG Auto Spec instrument.

(4*S*)-3-(2-Bromoallyl)-4-methoxymethoxymethyl-1,3-oxazolan-2-one 8 : To a mixture of NaH (0.96 g, 24.0 mmol) and THF (5 ml) was added dropwisely a solution of **7** [5] (2.35g, 10.0 mmol) in THF (5 ml) at -15°C. After stirring at rt for 15 hr, 2,3-dibromopropene (3.10 ml, 30.0 mmol) was added to the reaction mixture dropwisely. The mixture was stirred for further 15 hr, and then quenched with aq.satd. NH_4Cl and extracted with EtOAc. The extract was dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel and elution with EtOAc gave **8** (2.80g, 54 %) as an oil. $[\alpha]_D$ -16.48 (c 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.83 (d, 1H, *J* =1.1 Hz), 5.61 (d, 1H, *J* = 1.1 Hz), 4.57 (s, 2H), 4.38 (dd, 2H, *J* = 8.9, 8.8 Hz), 4.12 (dd, 1H, *J* = 8.8, 5.5 Hz), 3.99-3.93 (m, 1H), 3.91 (d, 1H, *J* =16.1 Hz), 3.63-3.54 (m, 2H), 3.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.0, 127.8, 119.9, 96.7, 69.3, 65.9, 55.7, 53.7, 50.5; IR (neat) 1752, 1435, 1044 cm^{-1}; EIMS *m/z* 279.9 (M^+); High resolution MS *m/z* calcd for $C_9H_{14}NO_4$ (M^+-Br): 200.0923. Found: 200.0927.

(4*S*)-3-(2-Bromoallyl)-4-hydroxymethyl-1,3-oxazolan-2-one 9 : A mixture of **8** (2.80g, 10.0mmol), Amberlist (200 mg) and MeOH (15ml) was stirred at 50°C for 15 hr. Amberlist was removed by filtration. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel. Elution with $CHCl_3$-MeOH (40:1) gave **9** (2.01g, 85%) as an oil. $[\alpha]_D$ -25.75 (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.88 (d, 1H, *J* =0.8 Hz), 5.63 (d, 1H, *J* =0.8 Hz), 4.38 (dd, 1H, *J* =9.0, 8.8 Hz), 4.40-4.31 (m, 2H), 4.25 (dd, 1H, *J* =8.8, 5.6 Hz), 3.96 (d, 1H, *J* =16.0 Hz), 3.90-3.84 (m, 1H), 3.75 (dd, 1H, *J* =12.1, 3.7 Hz), 3.59 (dd, 1H, *J* =12.1, 3.5 Hz), 3.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 158.9, 127.7, 120.5, 64.9, 60.5, 55.8, 50.3; IR (neat) 1736, 1439, 1256, 1093 cm^{-1}; EIMS*m/z* 235.9 (M^+). High resolution MS *m/z* calcd for $C_6H_7NO_2Br$ (M^+-CH_2OH): 203.9660. Found: 203.9664

Diethy{[(4*S*)-3-(2-bromoallyl)-2-oxo-1,3-oxazolan-4-yl]eth-1-enyl} phosphonate 10a : Dimethylsulfoxide (1.70 ml, 24.0 mmol) was added to a solution of oxalyl chloride (0.99ml, 11.5mmol) in CH_2Cl_2 (10 ml) at -78°C. After 15 min, a solution of **9** (2.36g, 10.0 mmol) in CH_2Cl_2 (10 ml) was slowly added to the mixture at -78°C. After stirring had been continued for 1hr at the same temperature, Et_3N (5.58ml, 40.0 mmol) was added to the mixture. The mixture was warmed to rt and kept for 1hr, and then a solution of Ph_3P=CHP(O)$(OEt)_2$ (10.30g, 25.0 mmol) in CH_2Cl_2 (20 ml) was added. After stirring at the same temperature for 8 hr, the solution was quenched with aq.satd. NH_4Cl. The aqueous layer was extracted with $CHCl_3$, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel. Elution with EtOAc: MeOH(20:1) gave **10a** (1.99g, 43 %) as an colorless oil. $[\alpha]_D$ +7.71 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.58-6.49 (m, 1H), 6.00-5.90 (m.1H), 5.78 (d, 1H, *J* =0.8 Hz), 5.62 (d, 1H, *J* =0.8 Hz), 4.49 (dd, 1H, *J* = 8.8, 8.7 Hz), 4.42-4.31 (m, 2H), 4.12-3.99 (m, 5H), 3.74 (d, 1H, *J* =15.8 Hz), 1.31 (t, 6H, *J* =7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 157.3, 145.6, 127.1, 125.0, 123.2, 120.8, 66.4, 62.3 (d, *J*cp=5.0 Hz), 57.6, 57.3, 16.4 (2 carbons); ^{31}P NMR ($CDCl_3$) δ 14.50 ; IR (neat) 1757, 1430, 1249, 1025 cm^{-1}; EIMS *m/z* 367.9 (M^+). 288.0 (M^+-Br); High resolution MS *m/z* calcd for $C_{12}H_{19}NO_5P$ (M^+-Br): 288.1001. Found: 288.1000.

Dipheny{[(4*S*)-3-(2-bromoallyl)-2-oxo-1,3-oxazolan-4-yl]eth-1-enyl}phosphonate 10b : This compound **10b** (1.49g, 38%) was obtained from **9** (2.36g, 10.0 mmol) and Ph_3P=CHP(O)$(OPh)_2$ (12.7g, 25.0 mmol) as a colorless oil according to the same conditions as above. $[\alpha]_D$ +3.69 (c 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50-6.86 (m, 10H), 6.66-6.45 (m, 1H), 6.14-5.84 (m, 1H), 5.30 (d, 1H, *J* =1.5 Hz), 5.23 (d, 1H, *J* =1.5 Hz), 4.22-4.08 (m, 2H), 4.08-3.93 (m, 1H), 3.75-3.54 (m, 1H), 3.35-3.24(m, 1H), ^{13}C NMR ($CDCl_3$) δ 157.1, 131.9 (4 carbons), 129.2 (2 carbons), 128.2 (4 carbons), 127.3, 125.5 (2 carbons),, 122.8, 120.4 (2 carbons), 66.4, 57.3, 50.2 ; ^{31}P NMR ($CDCl_3$) δ 19.60 ; IR (neat) 1762, 1489, 1188, 937 cm-1; EIMS *m/z* 463.1 (M^+), High resolution MS *m/z* calcd for $C_{20}H_{19}NO_5PBr$ (M^+): 463.0184. Found: 463.0184.

Diethyl(7*S*,7a*S*)-(6-methylene-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)methylphosphonate 11a

Radical cyclization of 10a in the presence of AIBN

To a solution of **10a** (0.37g, 1.0 mmol) in benzene (100 ml) at 80°C was added a solution of tributyltine hydride (0.40 ml, 1.50 mmol) and AIBN (16.4 mg,

0.1mmol) in benzene (100 ml) slowly over 4hr. After the addition, the mixture was further refluxed for 5 hr and then evaporated. The resulting residure was chromatographed on silica gel. After removal non-polar material by elution with hexane, elution with EtOAc: MeOH (50:1) gave **11a** (0.20g, 69%) as a colorless oil.

Radical cyclization of 10a in the presence of Et_3B

To a stirred mixture of **10a** (0.37g, 1.0 mmol), Et_3B (1.5ml, 1.0 M hexane solution) and toluene (100 ml) was slowly added a toluene solution of tributyltine hydride (0.40 ml, 1.50 mmol) over 2 hr at rt. After 12hr, the mixture was quenched with MeOH (2 ml) and worked up as above to give **11a** (0.24g, 83 %) as a colorless oil. $[\alpha]_D$ -20.62 (c 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.12 (d, 1H, *J* =1.6 Hz), 5.00 (d, 1H, *J* =1.6 Hz), 4.55 (dd, 1H, *J* =9.7, 7.7 Hz), 4.48 (dd, 1H, *J* =9.7, 3.4 Hz), 4.35-4.25 (m, 1H), 4.15-4.05 (m, 4H), 3.82-3.70 (m, 1H), 2.73-2.58 (m, 1H), 2.32-2.17 (m, 1H), 1.69-1.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 160.9, 107.9 (2 carbons), 68.1, 64.5, 62.1, 50.0, 42.7, 27.8, 26.4, 16.5, 16.4; ^{31}P NMR ($CDCl_3$) δ 28.13; IR (neat) 1757, 1397, 1231, 1024 cm-1; EIMS *m/z* 289 (M^+); High resolution MS *m/z* calcd for $C_{12}H_{20}NO_5P$ (M^+): 289.1079. Found: 289.1079.

Diphenyl(7*S*,7a*S*)-(6-methylene-3-oxotetrahydropyrrolo[1,2-*c*]-oxazol-7-yl)methylphosphonate 11b

Radical cyclization of 31b in the presence of AIBN

This compound **11b** (0.26g, 68 %) was obtained from **10b** (0.46g, 1.0 mmol) as a colorless oil according to the same conditions as above,

Radical cyclization of 10b in the presence of Et_3B

This compound **11b** (0.30g, 78 %) was obtained from **10b** (0.46g, 1.0 mmol) as a colorless oil according to the same conditions as above, $[\alpha]_D$ -3.99 (c 1.55, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.72-7.61 (m, 4H), 7.56-7.47 (m, 2H), 7.47-7.39 (m, 4H), 5.16 (d, 1H, *J* =1.8 Hz), 5.04 (d, 1H, *J* =1.8 Hz), 4.59 (dd, 1H, *J* = 9.9, 7.4 Hz), 4.53 (dd, 1H, *J* =9.9, 3.8 Hz), 4.38-4.30 (m, 1H), 3.96-3.88 (m, 1H), 3.81-3.73 (m, 1H), 2.92-2.80 (m, 1H), 2.69-2.56 (m, 1H), 2.09-1.96 (m, 1H) ; ^{13}C NMR ($CDCl_3$) δ 160.7, 132.9 (4 carbons), 130.1 (2 carbons), 128.6 (4 carbons), 125.7 (2 carbons), 108.4), (2 carbons), 68.2, 64.5 (2 carbons), 50.0, 42.5, ^{31}P NMR ($CDCl_3$) δ 21.60; IR (neat) 1756, 1489, 1438, 1190, 1120, 935, 722cm-1; EIMS *m/z* 385 (M+); High resolution MS *m/z* calcd for $C_{20}H_{20}NO_5P$ (M^+): 385.1079. Found: 385.1065.

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