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Enantioselective synthesis of both enantiomers of 2-amino-6-phosphonohexanoic acid [(*R*)- and (*S*)-AP6], a potent and specific agonist of AMPA receptor subtype

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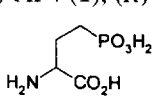
Abstract: The preparation of both enantiomers of 2-amino-6-phosphonohexanoic acid [(*R*)- and (*S*)-AP6] is described. The highly diastereoselective alkylation of imidazolidinones **4** and hydrolysis of the alkylated products [(2*R*,5*R*,1′*S*)-**6** and (2*S*,5*S*,1′*S*)-**6**] proceeds under relatively mild conditions to give the physiologically important, enantiopure aminophosphonic acids (*R*)-AP6 and (*S*)-AP6. © 1997 Elsevier Science Ltd

Introduction

Excitatory amino acids (EAA) are the most prevalent neurotransmitters in the mammalian central nervous system (CNS).[1] EAA receptors are thought to offer an abundant and varied opportunity to identify compounds useful to explore normal CNS function as well as to develop new therapeutics for the treatment of several pathological conditions affecting the brain, such as Alzheimer's Disease, Parkinsonism, and Huntington's Disease, as well as neuronal damage resulting from cerebral ischemia and epilepsy.[2]

Several studies have shown that phosphonate analogues of glutamic acid with side chain lengths of four to six carbon atoms are activators for the *N*-methyl-D-aspartate (NMDA) receptor site; for instance, (*R*)- and (*S*)-AP4 (**1**), (*R*)- and (*S*)-AP5 (**2**) and (*RS*)-AP6 (**3**), AP5 being the most potent.



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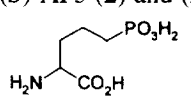

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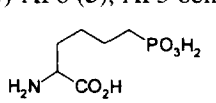

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Although a truly specific agonist for the AMPA-sensitized site has not been identified, data from previous studies suggest that the (*S*)-isomer of AP6 might be a particularly selective and potent agonist. Unlike NMDA receptors, however, the AMPA-sensitized site displays a preference for (*S*)- over (*R*)-isomers; thus, it seemed likely that (*S*)-AP6 might be uniquely selective for this site.[3] As a part of our program on the asymmetric synthesis of amino acids, we have recently described the preparation of biologically active α-amino-ω-phosphonocarboxylic acids.[4] In the present paper we report the synthesis of (*R*)- and (*S*)-AP6 in enantiopure form, using imidazolidinones (2*R*,1′*S*)-**4** and (2*S*,1′*S*)-**4**.

Results and discussion

The modified Seebach imidazolidinones **4** were prepared according to the procedure described by Juaristi *et al.*[4] In the present work, we used the diastereomeric pair (2*R*,1′*S*)-**4** and (2*S*,1′*S*)-**4**, resulting from the conversion of (*S*)-α-methylbenzylamine. Imidazolidinones (2*R*,1′*S*)-**4** and (2*S*,1′*S*)-**4** were then treated separately with LDA, and the resulting enolates were added to diethyl 4-bromobutylphosphonate (**5**). The desired alkylated products **6** were obtained with very high diastereoselectivity (>98%) as determined by ^{1}H NMR and ^{13}C NMR (Scheme 1). The trans relative configuration in the main product was established in analogy to previous work.[5]

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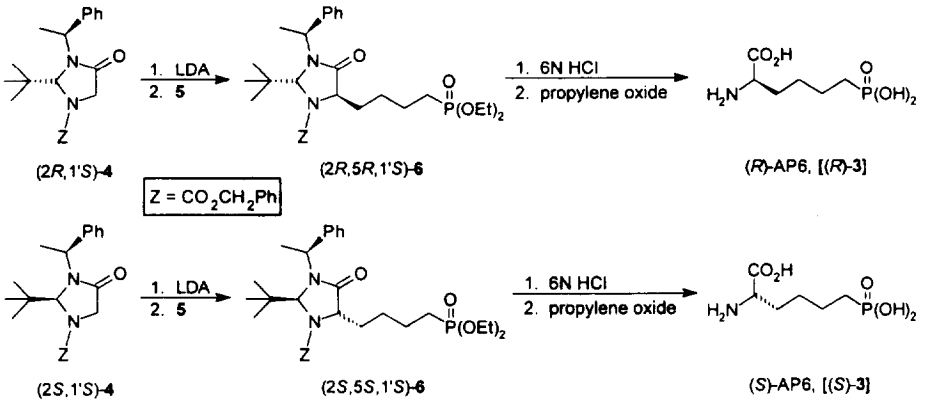

Scheme 1.

Adducts (2*R*,5*R*,1′*S*)-**6** and (2*S*,5*S*,1′*S*)-**6** were purified by flash chromatography to afford the pure derivatives in 62.1% and 61.4% yield, respectively. Hydrolysis to (*R*)-**3** and (*S*)-**3** proceeded conveniently under relatively mild conditions with 6N HCl, at 115°C during 16 h. Following extraction with CH_2Cl_2 and treatment with propylene oxide, we obtained enantiopure[6] (*R*)-(−)-AP6 and (*S*)-(+)-AP6, in 96.2% and 91.3% yields, respectively (Scheme 1).

Experimental[7]

Diethyl 4-bromobutylphosphonate (5)

In a 50 mL round-bottom Schlenk flask provided with magnetic stirrer and condenser, was placed 14.4 mL (25.9 g, 0.12 mol) of 1,4-dibromobutane and heated to 80°C before the addition of 5.2 mL (5.0 g, 30.1 mmol) of triethylphosphite. The reaction mixture was stirred at 80°C during 1 h, and then heated to 160°C for 5 h. The crude product was allowed to cool to room temperature and was purified by distillation in a Kugelrohr apparatus, bp 128°C/0.5 mm, as a viscous, colorless liquid in 78.2% yield. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (t, J=7.3 Hz, 6H, CH_2CH_3), 1.66–1.86 (m, 4H, CH_2CH_2P), 1.97 (p, J=6.6 Hz, 2H, $BrCH_2CH_2$), 3.42 (t, J=6.6 Hz, 2H, $BrCH_2$), 4.12 (p, J=7.3 Hz, 4H, CH_2CH_3). ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 15.9 (d, $^3J_{C/P}$=6.1 Hz, CH_2CH_3), 20.6 (d, $^2J_{C/P}$=4.89 Hz, CH_2CH_2P), 24.12 (d, $^1J_{C/P}$=141.6 Hz, CH_2P), 32.50 (d, $^3J_{C/P}$=14.5, $BrCH_2CH_2$), 32.85 (s, $BrCH_2$), 60.9 (d, $^2J_{C/P}$=6.1 Hz, CH_2CH_3). ^{31}P NMR (36.23 MHz, $CDCl_3$) δ 31.28.

(2R,5R,1′S)-1-Carbobenzyloxy-2-tert-butyl-3-(α-methylbenzyl)-5-(diethyl 4-butylphosphonate)-1,3-imidazolidin-4-one [(2R,5R,1′S)-6]

In a Schlenk flask was placed 15 mL of dry THF under nitrogen. The flask was inmersed in a dry ice–acetone bath at −78°C and then 0.2 mL (1.45 mmol) of diisopropylamine followed by 0.7 mL (1.45 mmol) of 2.0 M *n*-BuLi was added. The resulting solutions was stirred for 30 min before the addition of 0.5 g (1.32 mmol) of (2*R*,1′*S*)-**4** in 15 mL of THF. The resulting enolate solution was stirred 1 h and then 0.4 g (1.45 mmol) of bromide **5** was added. The reaction mixture was stirred for 1 h, quenched with 5 mL of saturated aqueous ammonium chloride, extracted with two 20 mL portions of CH_2Cl_2, dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (Hex-iPrOH, 95:5) to give 0.47 g (62.1% yield) of a colorless semisolid, $[\alpha]_D^{28}$=+57.0 (c=1, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (s, 9H, $C(CH_3)_3$), 1.31 (t, J=7.3 Hz, 6H, CH_2CH_3), 1.72 (d, J=7.3 Hz, CH_3CH), 0.95–2.10 (broad, 8H, $CH_2CH_2CH_2CH_2P$), 4.07 (p, J=7.3 Hz, 4H, CH_2CH_3), 4.16 (m, C(5)–**H**), 4.62 (q, J=7.3 Hz, CH_3CH), 5.08 (s, 2H, CH_2Ph), 5.11 (s, C(2)–**H**), 7.21–7.45 (m, 10H, H_{arom}). ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 16.50 (d, $^3J_{C/P}$=5.6 Hz, CH_2CH_3), 20.53 (s, CH_3CH), 22.30 (d, $^2J_{C/P}$=4.4 Hz, CH_2CH_2P), 23.94 (d, $^3J_{C/P}$=17.6 Hz, $BrCH_2CH_2$), 25.62 (d, $^1J_{C/P}$=141.0 Hz, CH_2P), 26.08 (s, $C(CH_3)_3$), 29.71 (s, $BrCH_2$), 40.53 (s, $C(CH_3)_3$), 59.66 (s, CH_3CH), 60.35 (s, C(5)),

61.42 (d, $^2J_{C/P}$=6.6 Hz, CH_2CH_3), 67.46 (s, CH_2Ph), 82.21 (s, C(2)), 127.10, 127.37, 128.46, 128.56, 128.67, 128.78, 135.77, 141.22 (C_{arom}), 153.80 (broad, NCOO), 172.86 (s, CO). ^{31}P NMR (36.23 MHz, $CDCl_3$) δ 31.91. Anal. Calcd. for $C_{31}H_{45}N_2O_6P$: C, 65.02; H, 7.92. Found: C, 64.87; H, 8.27.

(2S,5S,1′S)-1-Carbobenzyloxy-2-tert-butyl-3-(α-methylbenzyl)-5-(diethyl 4-butylphosphonate)-1,3-imidazolidin-4-one [(2S,5S,1′S)-6]

The same procedure described for the preparation of (2*R*,5*R*,1′*S*)-**6** was followed with 0.5 g (1.32 mmol) of (2*S*,1′*S*)-**4**, to afford 0.46 g (61.4% yield) of the desired product as a white solid, mp 64–65°C, $[\alpha]_D^{28}$=−22.7 (c=1.67, CH_2Cl_2). ^1H NMR (270 MHz, $CDCl_3$) δ 1.02 (s, 9H, $C(CH_3)_3$), 1.30 (t, J=6.6 Hz, 6H, CH_2CH_3), 2.02 (d, J=7.3 Hz, 6H, CH_3CH), 1.08–2.0 (broad, 8H, $CH_2CH_2CH_2CH_2P$), 4.03 (p, J=7.3 Hz, 4H, CH_2CH_3), 4.10 (m, C(5)–H), 4.53 (q, J=7.3 Hz, CH_3CH), 5.25 (s, C(2)–H), 5.28 (s, 2H, CH_2Ph), 7.15–7.55 (m, 10H, H_{arom}). ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 16.48 (d, $^3J_{C/P}$=5.6 Hz, CH_2CH_3), 16.80 (s, CH_3CH), 22.10 (d, $^2J_{C/P}$=4.4 Hz, CH_2CH_2P), 23.09 (d, $^3J_{C/P}$=19.9 Hz, $BrCH_2CH_2$), 25.36 (d, $^1J_{C/P}$=141.0 Hz, CH_2P), 26.26 (s, $C(CH_3)_3$), 32.71 (s, $BrCH_2$), 41.21 (s, $C(CH_3)_3$), 57.57 (s, CH_3CH), 60.26 (s, C(5)), 61.24 (d, $^2J_{C/P}$=5.5 Hz, CH_2CH_3), 67.34 (s, CH_2Ph), 81.10 (s, C(2)), 127.65, 127.97, 128.31, 128.46, 128.59, 135.77, 140.48 (C_{arom}), 154.0 (broad, NCOO), 172.57 (s, CO). ^{31}P NMR (36.23 MHz, $CDCl_3$) δ 31.95.

(R)-(−)-2-Amino-6-phosphonohexanoic acid [(R)-3]

In a glass ampoule provided with magnetic stirrer was placed 0.35 g (0.61 mmol) of (2*R*,5*R*,1′*S*)-**6** and 5 mL of 6N HCl. The ampoule was sealed and heated for 16 h in a oil bath at 115°C. The reaction mixture was then allowed to cool to room temperature, extracted with two 10 mL portions of CH_2Cl_2, the aqueous phase was concentrated and the residue suspended in 10 mL of anhydrous hot ethanol, allowed to cool to room temperature and treated dropwise with propylene oxide until the solution became turbid. At this point, the precipitated solid was filtered under vacuum and recrystallized from EtOH/H_2O (1:1) to afford 0.12 g (96.2% yield) of the corresponding (*R*)-AP6 as a white solid, mp 235°C (foam), $[\alpha]_D^{28}$=−18.0 (c=1, 6N HCl). ^1H NMR (270 MHz, D_2O) δ 1.40–1.85 (m, 6H, $CH_2CH_2CH_2P$), 1.85–2.15 (m, 2H, $CHCH_2$), 4.02 (t, J=5.9 Hz, CH). ^{13}C NMR (67.80 MHz, D_2O) δ 22.27 (d, $^2J_{C/P}$=4.4 Hz, CH_2CH_2P), 25.29 (d, $^3J_{C/P}$=16.5 Hz, $CH_2CH_2CH_2P$), 26.72 (d, $^1J_{C/P}$=133.3 Hz, CH_2P), 29.55 (s, $CHCH_2$), 53.47 (s, CH), 173.24 (s, CO). ^{31}P NMR (36.23 MHz, D_2O) δ 30.74.

(S)-(+)-2-Amino-6-phosphonohexanoic acid [(S)-3]

The same procedure described for the hydrolysis of (2*R*,5*R*,1′*S*)-**6** was carried out with 0.3 g (0.52 mmol) of (2*S*,5*S*,1′*S*)-**6** and 5 mL of 6N HCl to give 0.1 g (91.3% yield) of (*S*)-AP6 as a white solid, mp 235°C (foam), $[\alpha]_D^{28}$=+17.7 (c=1.12, 6N HCl). The ^1H, ^{13}C, and ^{31}P NMR spectra were similar to those for (*R*)-**3**.

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6. Under similar hydrolytic conditions, the lower homologues (*R*)- and (*S*)-AP5 were prepared in enantiopure form.[4]
7. For a description of general experimental data, see ref. 4.

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