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Stereoselective Synthesis of (1S,3R)-1-Aminocyclopentane-1,3-dicarboxylic Acid via C-H Insertion of Alkylidenecarbene

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Note

Stereoselective Synthesis of (1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic Acid *via* C–H Insertion of Alkylidenecarbene

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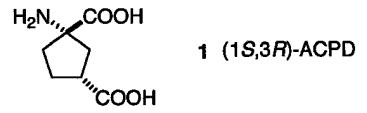
(1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic acid (ACPD), a potent agonist of metabotropic glutamate receptors, was synthesized from L-serine. The chiral quaternary center was constructed by C–H insertion of the alkylidenecarbene, this being generated by the reaction between lithiotrimethylsilyldiazomethane and the corresponding ketone.

Key words: metabotropic glutamate agonist; amino acid; chiral quaternary center; C–H insertion; alkylidenecarbene

1-Aminocyclopentane-1,3-dicarboxylic acid (ACPD) is a valuable compound as an agonist for studying the metabotropic glutamate receptor in the brain function.[1] (1*S*,3*R*)-ACPD (**1**) has been proved to be an active stereoisomer of (±)-*trans*-ACPD at metabotropic excitatory amino acid receptors.[2] Synthesis of all the stereoisomers of ACPD has been achieved based on optical resolution and separation of a diastereomeric mixture.[3,4] Two research groups have recently reported stereoselective syntheses of **1**,[5,6] whereby the 3-carboxyl group was introduced by substitution of the cyanide ion and subsequent hydrolysis. We describe here the concise stereoselective synthesis of **1** as an extension of our continuing studies to construct quaternary chiral centers by C–H insertion of alkylidenecarbenes.[7] A very similar approach to the simple analogue of **1** emerged in 1999; however, **1** itself was not attained.[8]

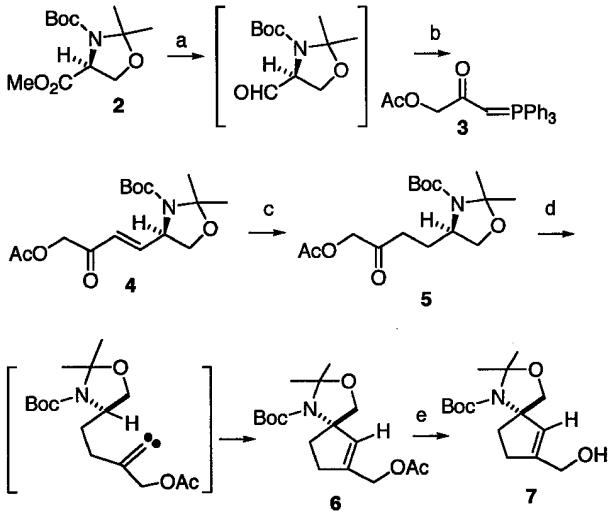
Methyl ester **2**, derived from L-serine,[9] was reduced with diisobutylaluminum hydride, and the crude aldehyde was treated with 2-oxo-3-(triphenyl-λ^5-phosphanylidene)propyl acetate (**3**).[10] Resulting α,β-unsaturated ketone **4** was hydrogenated over palladium on charcoal to give saturated ketone **5** in a high yield. The reaction between lithiotrimethylsilyldiazomethane and **5** gave cyclized product **6** *via* the generation of the alkylidenecarbene, this being followed by intramolecular 1,5 C–H insertion.[11] It is noteworthy that the keto group of **5** was selectively attacked by lithiotrimethylsilyldiazomethane which is known to react with esters.[12] Some of alcohol **7** and other products were also observed by thin-layer chromatography,[13] so the crude reaction products were treated with potassium carbonate in methanol and then purified. Alcohol **7** was obtained in a 50%–60% yield from **5**. The use of (dimethyl)diazomethylphosphonate[14] and t-BuOK for generating the carbene did not improve the yield.

The ^{1}H-NMR spectra of the cyclized products (**6** and **7**) were too complex to assign signals, even at 130°C in DMSO-d_6, due to rotamers attributed to the



1 (1*S*,3*R*)-ACPD

Fig. 1.



Scheme 1. (a) DIBAL-H, CH_2Cl_2, −78°C; (b) **3**, benzene, 60–70°C, 10 h (88% in 2 steps); (c) H_2, Pd/C, EtOAc (92%); (d) TMS(Li)CN_2, THF, −78–0°C, 2 h; (e) K_2CO_3, MeOH, rt, (50–60% in 2 steps).

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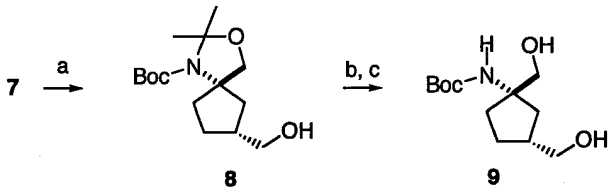
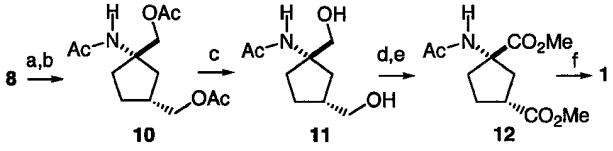


Scheme 2. (a) H_2, 4 atm, PtO_2, EtOAc (75%); (b) AcCl, MeOH, rt; (c) $(Boc)_2O$, 1 M NaOH (96% in 2 steps).



Scheme 3. (a) AcCl, MeOH, rt; (b) Ac_2O, Py, rt (65% in 2 steps); (c) KOH, MeOH, rt (66%); (d) CrO_3, H_2SO_4, acetone, rt, 5 h; (e) CH_2N_2, Et_2O (42% in 2 steps); (f) 6 M HCl, reflux (86%).

Boc group. We tried to remove the Boc group at this stage, but obtained only a complex mixture, because of the eminent instability of allylic alcohol **7** under acidic conditions.

Hydrogenation of **7** proceeded under 4.0 atom to afford saturated compound **8**. The stereoselectivity of this hydrogenation was not clear at this stage due to the presence of rotamers, although it was assumed that the hydrogen molecule came from the opposite side to that of the bulky Boc group. The stereochemistry of **8** became clear after it had been converted to compound **10**. After removing all the protecting groups, the amino group was again protected as a carbamate. Transformation of the diol to a diacid was attempted under various reaction conditions (conversion of diol **9** to the corresponding dialdehyde and then further oxidation, for example), but was unsuccessful due primarily to the lability of the Boc group under acidic conditions.

We therefore decided to change the protecting group of the amine. Treatment of **8** with acidic methanol and subsequent acetylation gave triacetate **10** as a single isomer. All signals of the ^{1}H-NMR spectrum could now be clearly assigned to structure **10**. It was disclosed here that the hydrogenation of **7** to **9** was highly stereoselective. Removal of two acetyl groups by basic hydrolysis gave diol **11**. Oxidation of **11** was attempted under many reaction conditions, the crude product being treated with diazomethane and purified as a dimethyl ester. Among the several conditions attempted, Jones oxidation employed at room temperature with subsequent esterification gave a moderate yield of **12**. Finally, the esters and acetamide of **12** were hydrolyzed with refluxing hydrochloric acid. Purification with ion-exchange resin gave (1*S*,3*R*)-ACPD, whose physical properties were identical with those reported.[3,5] The value for the optical rotation of synthetic ACPD was also satisfactory. We could not determine the enantiomeric excess of the synthetic intermediates,[15] although the ^{1}H-NMR spectra of **10**, **11** and the dimethyl ester of **1** with [Eu(hfc)$_3$] did not indicate the presence of other enantiomers.

Experimental

Melting points (mp) values are uncorrected. Optical rotation data were measured with a Horiba SEPA-200 polarimeter at ambient temperature. IR spectra were recorded by a Perkin-Elmer 1720 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded by either a Jeol JNM-GSX400 or Bruker ARX-400 spectrometer. Mass spectra (MS) and exact mass determinations were obtained with a JMX-700 MStation mass spectrometer. Analytical TLC was done on 1.5 × 5-cm precoated TLC plates (silica gel 60 F-254, 0.2 mm layer thickness) manufactured by E. Merck. Column chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM).

tert-Butyl (R)-4-(4-acetoxy-3-oxo-1-(E)-butenyl)-2,2-dimethyloxazolidine-3-carboxylate (4). To a solution of methyl ester **2** (13.55 g, 52.3 mmol) in dichloromethane was added a 1.0 M solution of diisobutylaluminum hydride in toluene (94.1 ml, 94 mmol) at −78°C under nitrogen. After stirring for 1 h, 10% aqueous sodium hydroxide was added to the reaction mixture at 0°C. The mixture was stirred for 15 min at rt and then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated. The crude aldehyde thus obtained was dissolved in anhydrous benzene, and the solution stirred with 2-oxo-3-(triphenyl-λ^5-phosphanylidene)propyl acetate (**3**; 27.54 g, 73.2 mmol) at 65–70°C overnight. The reaction was quenched with water, and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated. Purification by column chromatography on silica gel with hexane–ethyl acetate (3:1) as the eluent gave pure product **4** (11.87 g, 69%) as a mixture of rotamers. Oil; $[\alpha]_D^{26}$ −40° (*c* 0.84, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 1750 (O–C=O), 1694 (C=O and O–(C=O)–O), 1638 (C=C); NMR δ_H ($CDCl_3$): 1.42 and 1.49 (9H, each s, –C(CH_3)$_3$), 1.52 and 1.54 (3H, each s, one of –C(CH_3)$_2$), 1.60 and 1.65 (3H, each s, one of –C(CH_3)$_2$), 2.17 and 2.18 (3H, each s, OCOCH_3), 3.816 and 3.821 (1H, each d, J=9.2 Hz, one of N–CH–CH_2–O), 4.10–4.14 (1H, m, one of N–CH–CH_2–O), 4.44 and 4.56 (1H, each brs, N–CH–CH$_2$–O), 4.85 (2H, s, CH_2–OCOCH$_3$), 6.22 and 6.29 (1H, each d, J=15.9 and 16.3 Hz, CO–CH=CH–), 6.80–6.84 (1H, m, CO–CH=CH–); NMR δ_C ($CDCl_3$): 20.4, 23.4, 24.5, 26.4, 27.2, 28.3, 30.8, 58.2, 66.9, 67.1, 80.3, 80.8, 94.0, 94.6, 125.8, 145.2,

145.8, 151.4, 151.9, 170.1, 192.1, 206.8; MS *m/z* (%): 327 (M^+, 1), 312 (17), 271 (25), 256 (7), 254 (3), 212 (100), 194 (4), 170 (26), 152 (18), 96 (28), 57 (44); HRMS *m/z* (M^+): calcd. for $C_{16}H_{25}O_6N$, 327.1682; found, 327.1681.

tert-Butyl (R)-4-(4-acetoxy-3-oxobutyl)-2,2-dimethyloxazolidine-3-carboxylate (5). In the presence of 10% Pd/C (0.12 g), a solution of α,β-unsaturated ketone **4** (6.02 g, 18.17 mmol) in ethyl acetate was treated overnight with hydrogen under atmospheric pressure. After filtration to remove the catalyst, the solvent was evaporated. The residue was chromatographed on silica gel using hexane–ethyl acetate (3:1) to give saturated ester **5** (5.97 g, 99%). Oil; $[\alpha]_D^{26}$ −13° (*c* 1.45, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 1734 (O–C=O and O–(C=O)–O), 1685 (C=O); NMR δ_H ($CDCl_3$): 1.48 (9H, s, –C(CH_3)$_3$), 1.49 and 1.56 (6H, each s, –C(CH_3)$_2$), 1.92–1.97 (2H, m, N–CH–CH_2), 2.16 (3H, s, OCOCH_3), 2.47–2.62 (2H, m, CO–CH_2–CH_2), 3.58–4.09 (3H, m, N–CH–CH_2), 4.68 (2H, s, CH_2–OCOCH$_3$); NMR δ_C ($CDCl_3$): 20.4, 23.0, 24.3, 24.6, 26.6, 27.1, 27.3, 27.7, 28.4, 35.0, 35.4, 56.3, 65.3, 67.0, 67.4, 67.9, 80.2, 93.5, 94.1, 170.2, 203.2; MS *m/z* (%): 314 (M^+-15, 8), 269 (15), 254 (3), 228 (4), 214 (100), 198 (10), 169 (7), 154 (11), 138 (5), 112 (17), 83 (13), 57 (51); HRMS *m/z* (M^+-15): calcd. for $C_{15}H_{24}O_6N$, 314.1604; found, 314.1603.

tert-Butyl (S)-7-hydroxymethyl-2,2-dimethyl-1-aza-3-oxaspiro[4.4]non-6-ene-1-carboxylate (7). To a solution of trimethylsilyldiazomethane (a 2.0 M solution in hexane, 2.48 ml, 4.96 mmol) in THF (11 ml) was added a 1.54 M solution of butyllithium (3.21 ml, 4.95 mmol) at −78°C. After stirring for 1 h, a solution of ketone **5** (1.10 g, 3.3 mmol) in THF (5.5 ml) was added, and the mixture was stirred 0°C for 2 h. The reaction was quenched with aqueous ammonium chloride, and the solvent was evaporated. The aqueous residue was extracted with dichloromethane, and the organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude mixture (1.51 g) which was used in the next reaction.

The oil which contained acetate **6** was dissolved in methanol (16.5 ml) and treated with potassium carbonate (2.28 g, 16.5 mmol) at 0°C for 1.5 h. After filtration and evaporation, the residue was chromatographed on silica gel using hexane–ethyl acetate (3:1) to give alcohol **7** (528 mg, 56%) as a mixture of rotamers. Oil; $[\alpha]_D^{26}$ −33° (*c* 1.00, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 3447 (–OH), 1682 (C=O); NMR δ_H ($CDCl_3$): 1.40 and 1.46 (9H, s, –C(CH_3)$_3$), 1.49 and 1.51 (3H, each s, one of –C(CH_3)$_2$), 1.54 and 1.58 (3H, each s, one of –C(CH_3)$_2$), 2.05–2.57 (4H, m, –CH_2–CH_2), 3.69 and 3.72 (2H, each brs, N–CH–CH_2–O), 3.71 (2H, brs, –CH_2OH), 5.40 and 5.46 (1H, each brs, C=CH); NMR δ_C ($CDCl_3$): 24.4, 25.5, 25.9, 27.0, 28.4, 30.7, 33.9, 34.9, 61.6, 72.7, 73.6, 73.8, 74.2, 79.2, 79.9, 94.2, 94.8, 126.2, 127.1, 145.0, 146.5, 151.4, 151.9; MS *m/z* (%): 283 (M^+, 28), 268 (87), 225 (100), 210 (97), 194 (14), 166 (15), 150 (4), 83 (7), 57 (3); HRMS *m/z* (M^+): calcd. for $C_{15}H_{25}O_4N$, 283.1784; found, 283.1783.

tert-Butyl (5S,7R)-7-hydroxymethyl-2,2-dimethyl-1-aza-3-oxaspiro[4.4]nonane-1-carboxylate (8). In the presence of platinum oxide (6.0 mg), a solution of allylic alcohol **7** (299 mg, 1.054 mmol) in ethyl acetate (10.5 ml) was stirred under hydrogen at 400 kPa and rt for 6 h. After removing the catalyst by filtration, column chromatography on silica gel using hexane–ethyl acetate (2:1) as the eluent gave saturated alcohol **8** (225.3 mg, 75%) as a mixture of rotamers. Oil; $[\alpha]_D^{26}$ −14° (*c* 1.40, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 3441 (–OH), 1682 (C=O); NMR δ_H ($CDCl_3$): 1.48, 1.49, 1.52, and 1.55 (15H, each s, –C(CH_3)$_3$ and –C(CH_3)$_2$), 1.67–2.45 (7H, m, –CH_2–C–CH_2–CH_2 and OH), 3.60–4.09 (4H, m, N–C–CH_2–O and CH_2–OH); NMR δ_C ($CDCl_3$): 24.4, 24.6, 25.9, 26.1, 26.5, 27.1, 27.4, 28.35, 28.44, 28.7, 32.9, 36.8, 39.0, 40.6, 41.3, 65.3, 66.7, 67.0, 69.7, 76.2, 79.9, 94.1, 94.3, 151.4; MS *m/z* (%): 285 (M^+, 0.5%), 270 (6), 214 (13), 200 (5), 184 (4), 170 (59), 152 (76), 144 (56), 116 (83), 100 (43), 57 (100); HRMS *m/z* (M^+-15): calcd. for $C_{14}H_{24}O_4N$, 270.1705; found, 270.1705.

(1S,3R)-(3-Acetoxymethyl-1-acetylaminocyclopentyl)methyl acetate (10). To a solution of alcohol **8** in methanol (7.7 ml) was added acetyl chloride (0.39 ml, 5.51 mmol) at 0°C. The mixture was stirred at rt for 0.5 h, and the solvent was evaporated. The residue was successively treated with acetic anhydride (1.30 ml, 13.8 mmol), pyridine (1.11 ml, 13.7 mmol), and 4-dimethylaminopyridine (17 mg, 0.14 mmol) at rt overnight. The reaction was quenched with 1 M hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with brine and aqueous saturated sodium hydrogen carbonate, and dried over anhydrous sodium sulfate. Evaporation of the solvent and column chromatography on silica gel, using ethyl acetate as the eluent, gave triacetate **10** (244 mg, 65%). Oil; $[\alpha]_D^{26}$ −3° (*c* 2.25, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 3445 (N–H), 1735 (O–C=O), 1676 (N–C=O); NMR δ_H ($CDCl_3$): 1.56–2.03 (7H, m, –CH_2–C–CH_2–CH_2 and CH_2–O), 1.95 (3H, s, OCOCH_3), 2.06 (3H, s, OCOCH_3), 2.07 (3H, s, OCOCH_3), 2.08–2.34 (1H, m, –CH–CH$_2$–O), 4.00 (1H, dd, J=10.9, 6.8 Hz, one of –CH–CH_2–O), 4.05 (1H, dd, J=10.9, 7.2 Hz, one of –CH–CH_2–O), 4.25 (2H, s, one of –C–CH_2–O), 5.77 (1H, s, N–H); NMR δ_C ($CDCl_3$): 20.8, 20.9, 24.0, 27.4, 34.5, 37.3, 38.2, 63.0, 66.6, 67.7, 169.8, 170.9, 171.1; MS *m/z* (%): 256 (M^+-15, 14), 228 (14), 211 (12), 198 (91), 185 (13), 156 (58),

138 (93), 129 (19), 110 (27), 96 (100), 92 (28), 60 (37), 57 (28).

N-[(1S,3R)-1,3-Bis(hydroxymethyl)cyclopentyl] acetamide (11). To a suspension of dry potassium carbonate (186 mg, 1.35 mmol) in methanol (2.3 ml) was added a solution of acetate **10** in methanol (1.1 ml) at 0°C. The mixture was stirred at rt for 1.5 h and then filtered. Evaporation of the solvent and column chromatography on silica gel, using acetone as the eluent, gave diol **11** (83 mg, 66%). Oil; $[\alpha]_D^{26}$ $-10°$ (*c* 0.60, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 3445 (N–H), 3339 (O–H), 1653 (N–C=O); NMR δ_H ($CDCl_3$): 1.56–1.66 and 1.74–1.85 (each 2H, each m, $-CH_2-CH_2-$), 1.98 (3H, s, $N-COCH_3$), 2.00–2.03 (2H, m, $C-CH_2-CH$), 2.30–2.33 (1H, m, $CH-CH_2-O$), 3.58 (1H, d, $J=11.4$ Hz, one of $N-C-CH_2-O$), 3.62 (1H, dd, $J=9.8$, 4 Hz, one of $CH-CH_2-O$), 3.65 (1H, dd, $J=9.8$, 4.6 Hz, one of $CH-CH_2-O$), 3.75 (1H, d, $J=11.4$ Hz, one of $N-C-CH_2-O$), 5.26 (1H, br, OH), 6.71 (1H, brs, NH); NMR δ_C ($CDCl_3$): 23.8, 26.4, 35.0, 39.0, 39.2, 65.4, 66.8, 69.3, 171.7; MS *m/z* (%): 156 (M^+-29, 72), 128 (7), 126 (7), 114 (100), 96 (41), 79 (13), 72 (16), 59 (26); HRMS *m/z* (M^+-29): calcd. for $C_8H_{14}O_2N$, 156.1025; found, 156.1024.

Dimethyl (1S,3R)-1-Acetylaminocyclopentane-1,3-dicarboxylate (12). Jones reagent (2.75 M) was added to a solution of diol **11** (30 mg, 0.16 mmol) in acetone (0.8 ml) until the red color persisted (ca. 0.5 ml). The mixture was stirred at rt for 5 h, and then the reaction was quenched with solid sodium hydrogen sulfite. The top clear layer was treated with diazomethane in ether, and evaporated. Column chromatography on silica gel using ethyl acetate as the eluent, gave diester **12** (16 mg, 42%). Oil; $[\alpha]_D^{26}$ $-3.7°$ (*c* 1.50, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 3446 (N–H), 1734 (O–C=O), 1675 (N–C=O); NMR δ_H ($CDCl_3$): 1.98 (3H, s, $N-COCH_3$), 2.14–2.38 (6H, m, $CH_2-C-CH_2CH_2$), 3.08 (1H, m, CO–CH), 3.71 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 6.62 (1H, s, NH); NMR δ_C ($CDCl_3$): 23.0, 28.5, 35.9, 39.8, 42.0, 52.2, 52.6, 65.7, 169.8, 173.3, 177.3; MS *m/z* (%): 243 (M^+, 12), 212 (7), 184 (76), 170 (26), 142 (100), 124 (20), 82 (72); HRMS *m/z* (M^+): calcd. for $C_{11}H_{17}O_5N$, 243.1107; found, 243.1106.

(1S,3R)-1-Aminocyclopentane-1,3-dicarboxylic acid (1). Diester **12** (18 mg, 0.074 mmol) was treated with 6 M hydrochloric acid under the refluxing condition for 5 h. After evaporating the water, the residue was purified by ion-exchange chromatography on Dowex 50WX8-100 eluted with 2 M aqueous NH_3[6] to give dicarboxylic acid **1** (11 mg, 86%). White solid; $[\alpha]_D^{23}$ $-8.5°$ (*c* 1.65, H_2O) {lit.[3] $[\alpha]_D^{20}$ $-6.9°$ (*c* 1.0, H_2O)}; NMR δ_H (D_2O): 1.96–2.03 (2H, m, two of $-CH_2-CH_2-$), 2.11 (1H, dd, $J=4.2$, 14.5 Hz, one of $CH-CH_2-C-N$), 2.23–2.33 (2H, m, two of $-CH_2-CH_2-$), 2.37 (1H, dd, $J=8.5$, 14.5 Hz, one of $CH-CH_2-C-N$), 2.99–3.06 (1H, m, $CH-COOH$); NMR δ_C ($CDCl_3$): 31.3, 36.9, 41.0, 48.0, 68.1, 178.5, 185.9.

References

1) McLennan, H. and Liu, J. R., The action of six antagonists of the excitatory amino acids on neurons of the rat spinal cord. *Exp. Brain Res.*, **45**, 151–156 (1982); Schoepp, D. D. and Conn, P. J., Metabotropic glutamate receptors in brain function and pathology. *Trends Pharmacol. Sci.*, **14**, 13–20 (1993).
2) Schoepp, D. D., Johnson, B. G., True, R. A., and Mon, J. A., Comparison of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicaroxylic acid (1*S*,3*R*-ACPD) and 1*R*,3*R*-ACPD-stimulated brain phosphoinositide hydrolysis. *European Journal of Pharmacology—Molecular Pharmacology Section*, **207**, 351–353 (1991).
3) Curry, K., Peet, M. J., Magnuson, D. S. K., and McLennan, H., Synthesis, resolution, and absolute configuration of the isomers of the neuronal excitant 1-amino-1,3-cyclopentanedicarboxylic acid. *J. Med. Chem.*, **31**, 864–867 (1988).
4) Trigalo, P., Buisson, D., and Azerad, R., Chemoenzymatic synthesis of conformationally rigid glutamic acid analogues. *Tetrahedron Lett.*, **47**, 6109–6112 (1988).
5) Ma, D., Ma, J., and Dai, L., Stereospecific synthesis of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid, a selective agonist of metabotropic glutamate receptors. *Tetrahedron Asymmetry*, **8**, 825–827 (1997).
6) Hodgson, D. M., Thompson, A. J., Waldman, S., and Keats, C. J., On the Possibility of carbamate-directed hydroboration. An approach to the asymmetric synthesis of 1-aminocyclopentane-1,3-dicarboxylic acid. *Tetrahedron*, **55**, 10815–10834 (1999).
7) Ohira, S., Yoshihara, N., and Hasegawa, T., Synthesis of (−)-gleenol *via* C–H insertion reaction of alkylidenecarbene. *Chem. Lett.*, 739–740 (1998); Ohira, S., Ida, T., Moritani, M., and Hasegawa, T., Synthesis of (−)-malyngolide using reactions of alkylidenecarbenes. *J. Chem. Soc., Perkin Trans. I*, 293–297 (1998); Ohira, S., Noda, I., Mizobata, T., and Yamato, M., Synthesis of tertiary alcohol from secondary alcohol *via* intramolecular C–H insertion of alkylidenecarbene. *Tetrahedron Lett.*, **36**, 3375–3376 (1995); Ohira, S., Ishi, S., Shinohara, K., and Nozaki, H., C–H Insertion method for the chiral tertiary alcohol: Formal synthesis of (−)-frontalin. *Tetrahedron Lett.*, **31**, 1039–1040 (1990).
8) Gabaitsekgosi, R. and Hayes, C. J., Alkylidene carbene C–H insertion strategy for the enantioselective synthesis of α,α-dialkyl-α-amino acids. *Tetrahedron Lett.*, **40**, 7713–7716 (1999).
9) Garner, P. and Park, J. M., 1,1-Dimethylethyl (*S*)- or (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate: a useful serinal derivative. *Org. Synth.*, **70**, 18–26 (1992).

10) Kim, K. S. and Szarek, W. A., Synthesis of 3′,7′-anhydrooctose nucleosides related to the ezomycins and the octosyl acids. *Can. J. Chem.*, **59**, 878–888 (1981).
11) Shioiri, T. and Aoyama, T., Trimethyldiazomethane: a useful reagent for generating alkylidene carbenes and its application to organic synthesis. *Synth. Org. Chem., Jpn.*, **54**, 918–928 (1996); Ohira, S., Okai, K., and Moritani, T., Generation of alkylidenecarbenes by the alkenation of carbonyl compounds with lithiotrimethylsilyldiazomethane. *J. Chem. Soc., Chem. Commun.*, 721–722 (1992).
12) Aoyama, T. and Shioiri, T., New methods and reagents in organic synthesis. 31. Lithium trimethylsilyldiazomethane: a new synthon for the preparation of tetrazoles. *Chem. Pharm. Bull.*, **30**, 3450–3452 (1982).
13) We presume that those byproducts were produced by the reaction between the excess reagent and the acetyl group of **6**.
14) Gilbert, J. C., Giamalva, D. H., and Weerasooriya, U., Intramolecular carbon-hydrogen insertions of alkylidenecarbenes. 1. Selectivity. *J. Org. Chem.*, **26**, 5251–5256 (1983); Ohira, S., Methanolysis of dimethyl(1-diazo-2-oxopropyl)phosphonate: generation of dimethyl(diazomethyl)phosphonate and reaction with carbonyl compounds. *Synth. Commun.*, **19**, 561–564 (1989).
15) Scince all intermediates except **10**, **11** and the dimethyl ester of **1** were rotameric mixtures, we did not examine their optical purity. Attempts to convert **10** to the bis MTPA ester under various conditions were unsuccessful.