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**CONCISE AND SHORT SYNTHESIS OF FUNCTIONALIZED
5,6-DIHYDROPYRIDIN-2-ONES BY MEANS OF
PALLADIUM(0)-CATALYZED CROSS-COUPLING OF KETENE
AMINAL PHOSPHATES[†]**

**Haruhiko Fuwa,^{1*} Akane Kaneko,¹ Yasuaki Sugimoto,² Taisuke Tomita,²
Takeshi Iwatsubo,² and Makoto Sasaki^{1*}**

¹Laboratory of Biostructural Chemistry, Graduate School of Life Sciences, Tohoku University, 1-1 Tsutsumidori-amamiya, Aoba-ku, Sendai 981-8555, Japan and ²Department of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: masasaki@bios.tohoku.ac.jp; hfuwa@bios.tohoku.ac.jp

Abstract – A concise and short synthetic entry to 5,6-dihydropyridin-2-one derivatives has been developed by means of palladium(0)-catalyzed cross-coupling of cyclic ketene aminal phosphates.

γ -Secretase is a membrane-bound macromolecular complex comprised of Presenilin, Nicastrin, Pen-2 and Aph-1, which is responsible for the proteolytic processing of amyloid precursor protein to generate amyloid β (A β) peptides. Since the neurodegenerative disorder Alzheimer's disease (AD) is pathologically characterized by the extensive extracellular deposition of A β as senile plaques and intracellular deposition of tau proteins as neurofibrillary tangles in cerebral cortices, regulation of the A β levels by γ -secretase inhibitors is considered as mechanism-based therapeutics for AD.¹

We have previously reported the discovery of structurally novel γ -secretase inhibitors GS155 (**1**) and GS416 (**2**) from our in-house synthetic library of natural products intermediates (Figure 1).^{2,3} The common structural feature of these molecules is the 6-membered cyclic enone core arranged with two aromatic rings, which is important for displaying the sufficient inhibitory activity. It was envisioned that functionalized 5,6-dihydropyridin-2-one derivatives (**3**) would be interesting structural alternatives to GS155 and GS416 (**1** and **2**, respectively).

[†] Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

A number of 5,6-dihydropyridin-2-one derivatives have been reported to be important intermediates for the synthesis of conformationally constrained peptidomimetics, piperidine alkaloids and aza-sugars.⁴ Development of an efficient method for the synthesis of functionalized 5,6-dihydropyridin-2-one derivatives is, therefore, a synthetically demanding objective. As demonstrated by us⁵ and others,^{6,7} functionalization of medium-sized lactones and lactams by means of palladium(0)-catalyzed cross-coupling reactions of the corresponding ketene acetal and aминаl phosphates is a powerful approach for the synthesis of structurally complex natural products and biologically active small molecules of pharmaceutical interest. Herein, we describe the development of a concise and short synthetic entry to derivatives represented by compound (**3**) by means of palladium(0)-catalyzed cross-coupling reaction of cyclic ketene аминаl phosphates.

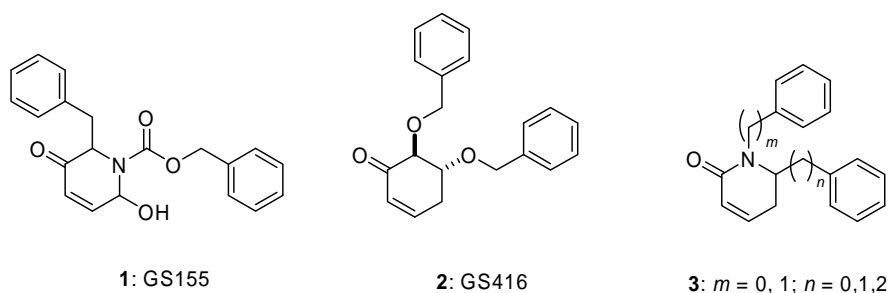
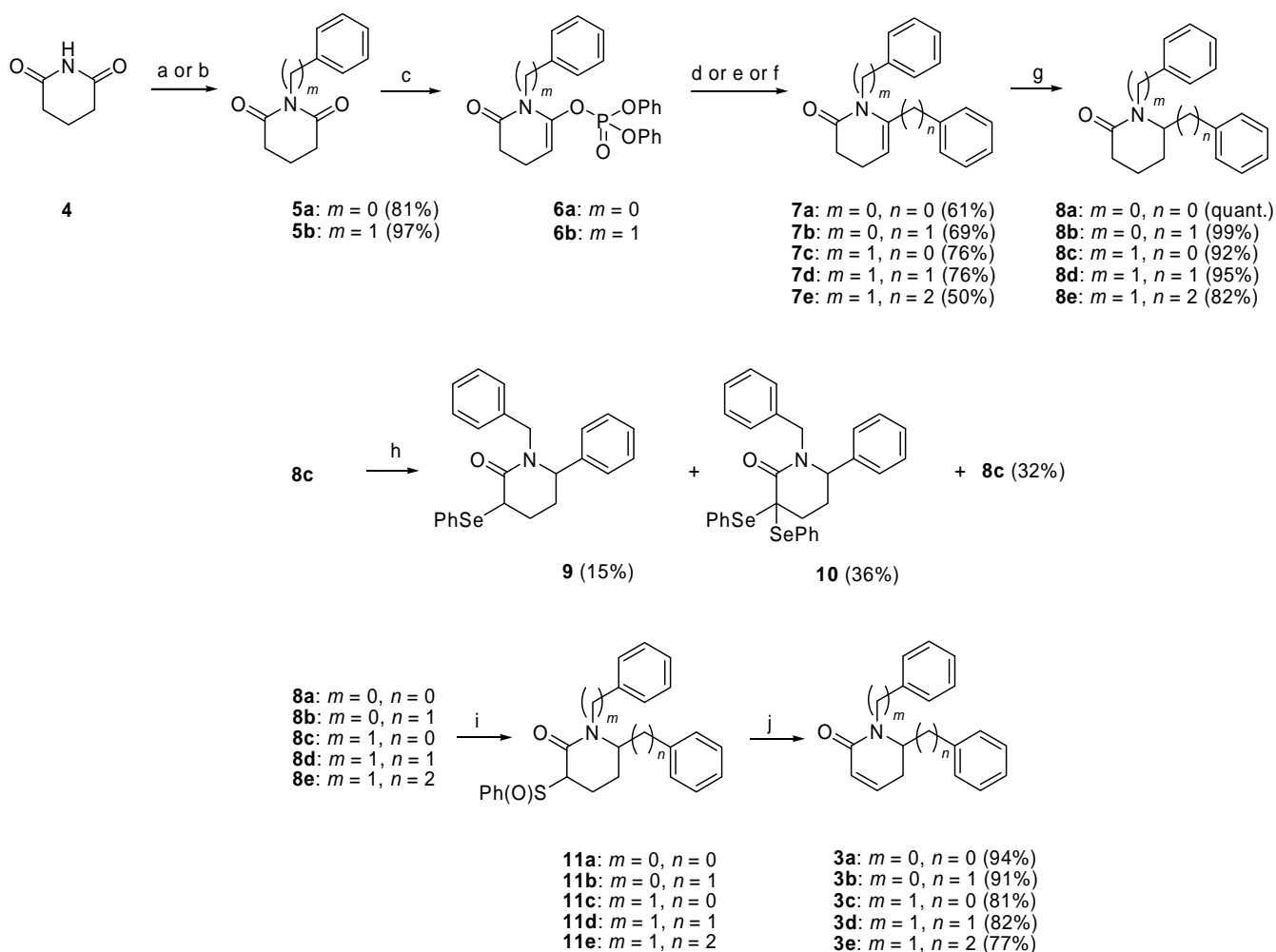


Figure 1. Structures of GS155 (**1**), GS416 (**2**) and functionalized 5,6-dihydropyridin-2-one derivatives (**3**).

As illustrated in Scheme 1, our synthetic approach for functionalized 5,6-dihydropyridin-2-one derivatives (**3**) utilized palladium(0)-catalyzed cross-coupling reactions of ketene аминаl phosphates (**6a,b**), which enables divergent synthesis of analogous molecules. The synthesis commenced with alkylation/arylation⁸ of glutarimide (**4**) to give imides (**5a,b**),⁹ which were exposed to 1.1 equiv. of LiHMDS in the presence of 1.2 equiv. of diphenylphosphoryl chloride (THF, -78 °C to room temperature) to provide ketene аминаl phosphates (**6a,b**). Using a series of organometallic nucleophiles under palladium(0)-catalyzed conditions, we were able to incorporate an aryl, benzyl and alkyl group to the six-membered ring, giving rise to enecarbamates (**7a-e**). Thus, treatment of **6a,b** with phenyl boronic acid in the presence of Cs_2CO_3 and $\text{Pd}(\text{PPh}_3)_4$ in DMF/ H_2O at room temperature¹⁰ afforded **7a**¹¹ and **7c** in good yields. In a similar manner, enecarbamates (**7b,d** and **7e**) were synthesized by using an organozinc reagent prepared from benzyl bromide and activated Zn powder [$\text{PdCl}_2(\text{PPh}_3)_2$, DMF, room temperature]¹² and an alkylborane derived from styrene [Cs_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, DMF/ H_2O , room temperature], respectively. Hydrogenation of the enecarbamates (**7a-e**) [H_2 (0.8 MPa), Pd/C] afforded tetrahydropyridones (**8a-e**).¹³ For the installation of the double bond, we first examined the application of standard selenium chemistry. However, upon treatment of **8c** with LiHMDS (1.5 equiv) followed by PhSeCl (1.3 equiv), the desired **9** was produced in only 15% yield. Significant amount of bis-selenylated

10 (36% yield) was isolated as a byproduct and **8c** (32% yield) was also recovered. Although we screened several other reaction conditions, including the examination of other bases (e.g. LDA, KHMDS), source of selenide (e.g. PhSeBr) and their molar amounts, we could not improve the yield of **9** and formation of **10** as a byproduct was always accompanied and predominated. These disappointing outcomes led us to investigate an alternative method, which involves incorporation of a sulfoxide group. Thus, exposure of **8a-e** to KH and methyl benzenesulfinate gave sulfoxides (**11a-e**) as a mixture of diastereomers, which without separation were heated in toluene at reflux temperature to affect thermal elimination of the sulfoxide, giving rise to the desired 5,6-dihydropyridin-2-ones (**3a-e**)^{14,15} in 77–94% yields for the two steps. Unfortunately, preliminary biological evaluation revealed that compounds (**3c-e**) were inactive at 0.1–10 μM range in our *in vitro* assay.¹⁶ Currently, further detailed evaluation of **3a-e** at higher concentrations is in progress.



Scheme 1. Reagents and conditions: (a) BnBr, K_2CO_3 , $n\text{-Bu}_4\text{NI}$, acetone, rt; (b) PhB(OH)_2 , Cu(OAc)_2 , Et_3N , 4Å molecular sieves, CH_2Cl_2 , rt; (c) LiHMDS, THF, -78°C ; then $(\text{PhO})_2\text{P(O)Cl}$, -78°C to rt; (d) PhB(OH)_2 , Cs_2CO_3 , $\text{Pd(PPh}_3)_4$, DMF/ H_2O , rt; (e) benzylzinc bromide, $\text{PdCl}_2(\text{PPh}_3)_2$, DMF, rt; (f) styrene, 9-BBN-H, THF, rt; then **6b**, Cs_2CO_3 , $\text{Pd(PPh}_3)_4$, DMF/ H_2O , 50°C ; (g) H_2 (0.8 MPa), 10% Pd/C, EtOH, rt; (h) LiHMDS, THF, -78°C ; then PhSeCl, -78°C ; (i) KH, methyl benzenesulfinate, THF, reflux; (j) Na_2CO_3 , toluene, 110°C .

In conclusion, a concise and short synthetic entry to functionalized 5,6-dihydropyridin-2-one derivatives by palladium(0)-catalyzed cross-coupling reactions of ketene amination phosphates has been developed. Established chemistry would enable us to synthesize a series of structural analogues in a divergent manner. Further application of the present strategy to the synthesis of other types of nitrogen-containing heterocycles is currently under investigation.

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 - Selected data for compounds (**3a-e**). **3a**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.34—7.11 (m, 10H), 6.41 (dddd, $J = 9.6, 6.0, 2.7, <1$ Hz, 1H), 6.17 (ddd, $J = 9.6, 2.7, <1$ Hz, 1H), 5.08 (dd, $J = 7.5, 2.1$ Hz, 1H), 3.20 (dddd, $J = 18.0, 7.5, 2.7, 2.7$ Hz, 1H), 2.61 (dddd, $J = 18.0, 6.0, 2.7, <1$ Hz, 1H); HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{16}\text{NO}$ $[(\text{M} + \text{H})^+]$ 250.1232, found 250.1233. **3b**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.44—7.16 (m, 8H), 7.01—6.98 (m, 2H), 6.53 (m, 1H), 6.12 (dd, $J = 9.9, 3.0$ Hz, 1H), 4.09 (m, 1H), 3.02 (dd, $J = 13.5, 4.5$ Hz, 1H), 2.92 (dd, $J = 13.5, 10.5$ Hz, 1H), 2.64 (dddd, $J = 18.0, 6.0, 2.1, 2.1$ Hz, 1H), 2.28 (ddd, $J = 18.0, 6.0, 2.1$ Hz, 1H); HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{18}\text{NO}$ $[(\text{M} + \text{H})^+]$ 264.1388, found 264.1389. **3c**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.35—7.20 (m, 8H), 7.16—7.13 (m, 2H), 6.30 (dddd, $J = 9.3, 5.7, 2.4, <1$ Hz, 1H), 6.10 (ddd, $J = 9.6, 2.4, <1$ Hz, 1H), 5.61 (d, $J = 15.0$ Hz, 1H), 4.56 (dd, $J = 6.6, <1$ Hz, 1H), 3.49 (d, $J = 15.0$ Hz, 1H), 2.90 (dddd, $J = 18.0, 7.8, 2.7, 2.7$ Hz, 1H), 2.43 (dddd, $J = 18.0, 6.0, 1.8, <1$ Hz, 1H); HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{18}\text{NO}$ $[(\text{M} + \text{H})^+]$ 264.1388, found 264.1386. **3d**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.34—7.21 (m, 8H), 7.07—7.04 (m, 2H), 6.43 (dddd, $J = 9.6, 6.3, 1.5, 1.5$ Hz, 1H), 6.06 (apparent dd, $J = 9.6, 3.0$ Hz, 1H), 5.37 (d, $J = 15.0$ Hz, 1H), 3.66 (d, $J = 15.0$ Hz, 1H), 3.55 (m, 1H), 2.94 (dd, $J = 13.2, 5.4$ Hz, 1H), 2.78 (dd, $J =$

13.2, 9.6 Hz, 1H), 2.36 (dddd, $J = 18.0, 6.9, 2.7, 2.7$ Hz, 1H), 2.12 (m, 1H); HRMS (FAB) calcd for $C_{19}H_{20}NO [(M + H)^+]$ 278.1545, found 278.1542. **3e**: 1H NMR (300 MHz, $CDCl_3$) δ 7.34—7.17 (m, 6H), 7.13—7.08 (m, 4H), 6.41 (m, 1H), 5.99 (dd, $J = 9.6, 3.0$ Hz, 1H), 5.35 (d, $J = 14.7$ Hz, 1H), 3.72 (d, $J = 14.7$ Hz, 1H), 3.33 (m, 1H), 2.64 (ddd, $J = 14.1, 9.3, 5.1$ Hz, 1H), 2.53—2.39 (m, 2H), 2.26 (m, 1H), 2.03 (m, 1H), 1.84 (m, 1H); HRMS (FAB) calcd for $C_{20}H_{22}NO [(M + H)^+]$ 292.1701, found 292.1707.

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