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Highly efficient synthesis of medium-sized lactams via intramolecular Staudinger–aza-Wittig reaction of ω-azido pentafluorophenyl ester: synthesis and biological evaluation of LY411575 analogues

Haruhiko Fuwa,* Yumiko Okamura, Yuichi Morohashi, Taisuke Tomita, Takeshi Iwatsubo, Toshiyuki Kan, Tohru Fukuyama and Hideaki Natsugari*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—A highly efficient method for the synthesis of medium-sized lactams based on intramolecular Staudinger–aza-Wittig reaction of *ω*-azido pentafluorophenyl ester has been developed. A variety of 7–10 membered lactams were synthesized in excellent yields. Application of the method to the synthesis of analogues of a potent γ-secretase inhibitor LY411575 and their biological evaluation are also described.

Alzheimer's disease (AD), a major dementing neurodegenerative disorder, is currently a serious public health problem in aging society and over four millions of victims are annually reported in US alone.[1] The exact pathogenic mechanism of AD is still unveiled, though many factors have been suggested on the basis of pathological and pharmacological studies. AD is hallmarked clinically by progressive cognitive decline and pathologically by deposition of extracellular proteinaceous plaques composed of 40–42 amino acid amyloid-β (Aβ) peptides in celebral cortices. Since Aβ is produced from amyloid precursor protein (APP) through proteolytic processing by two types of membrane associated aspartic proteases termed β- and γ-secretase, inhibition of 'amyloidogenic' APP processing by these secretases are predicted to be intriguing targets toward prevention and cure of AD.

The γ-secretase inhibitor LY411575 (**1**, IC_{50}<1 nM in HEK cells), discovered by researchers at Eli Lilly, is one of the most potent γ-secretase inhibitors reported to date (Fig. 1).[2] During the course of structure–activity relationship (SAR) studies on **1**, practical synthesis of medium-sized lactams via lactamization of the corresponding ω-amino acids turned out to be rather challenging than anticipated. An inherent problem associated with such conventional approach is the difficulty of handling and purification of ω-amino acid, due primarily to its zwitterionic nature. Very recently, we found that the 13-membered lactam ring could be constructed in an efficient manner based on intramolecular Staudinger–aza-Wittig reaction[3–5] of ω-azido pentafluorophenyl (pfp) ester (Scheme 1).[6] Thus, treatment of ω-azido pfp ester **2** with phosphine produces iminophosphorane **3**, which undergoes intramolecular aza-Wittig reaction to give iminoether **4**. Subsequent hydrolysis affords lactam ring **5**. It occurred to us that this approach might serve as a general strategy for the construction of synthetically challenging medium-sized lactam rings. Herein we describe a highly efficient and

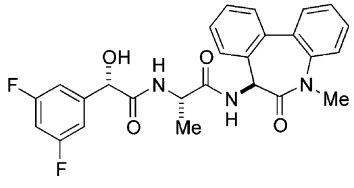

Figure 1. Structure of LY411575 (**1**).

Keywords: Medium-sized lactams; Staudinger reaction; Aza-Wittig reaction; γ-Secretase inhibitor; Structure–activity relationship.
* Corresponding authors. Tel.: +81-3-5841-4775; fax: +81-3-5841-4775; e-mail addresses: hfuwa@mol.f.u-tokyo.ac.jp; natsu@mol.f.u-tokyo.ac.jp

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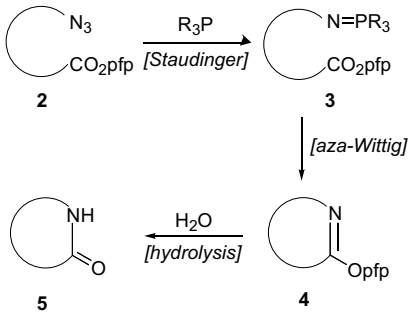
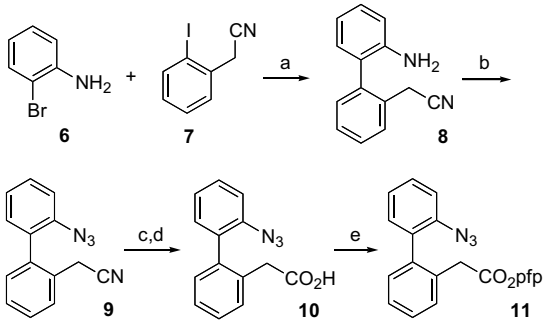


Scheme 1. Reaction pathway of intramolecular Staudinger–aza-Wittig reaction of ω-azido pentafluorophenyl (pfp) ester.

convenient method for the synthesis of medium-sized lactams via intramolecular Staudinger–aza-Wittig reaction of ω-azido pfp ester, and its application to the generation and biological evaluation of LY411575 analogues.

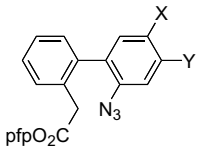
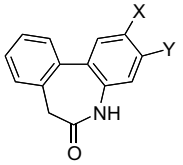
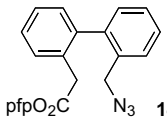
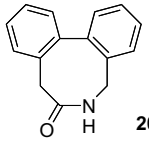
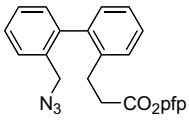
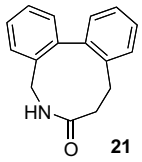
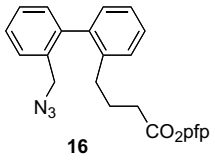
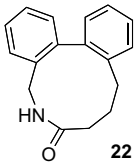
Synthesis of a representative ω-azido pfp ester **11** is outlined in Scheme 2. The biaryl moiety of **11** was constructed via borylation–Suzuki–Miyaura coupling protocol.[7,8] Thus, pinacol borylation of 2-bromoaniline **6** followed by in situ Suzuki–Miyaura coupling with aryl iodide **7** in the presence of $Ba(OH)_2{\cdot}8H_2O$ afforded coupling product **8**[8b] in quantitative yield. Diazotization of **8** under standard conditions followed by treatment with NaN_3 gave azide **9**. Reduction of the nitrile group within **9** and $NaClO_2$ oxidation of the derived aldehyde gave rise to carboxylic acid **10** in 57% yield (three steps). Coupling of **10** with pentafluorophenol then afforded **11**. In general, ω-azido pfp esters are stable enough for standard aqueous workup, flash chromatography and storage. Thus, we did not experience any difficulties upon handling and purification of **11**–**16** (Table 1).

To validate the scope and generality of intramolecular Staudinger–aza-Wittig reaction of ω-azido pfp ester, its application to a variety of substrates has been performed and the results are summarized in Table 1. Based



Scheme 2. Reagents and conditions: (a) **6**, pinacolborane, Et_3N, $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl, dioxane, 80 °C then **7**, $Ba(OH)_2{\cdot}8H_2O$, H_2O, dioxane, 100 °C, quant; (b) $NaNO_2$, aq. HCl, THF, 0 °C then NaN_3, 0 °C → rt; (c) DIBALH, CH_2Cl_2, −78 °C; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O (4:1), 0 °C → rt, 57% for three steps; (h) Pentafluorophenol, DCC, CH_2Cl_2, rt, quant.

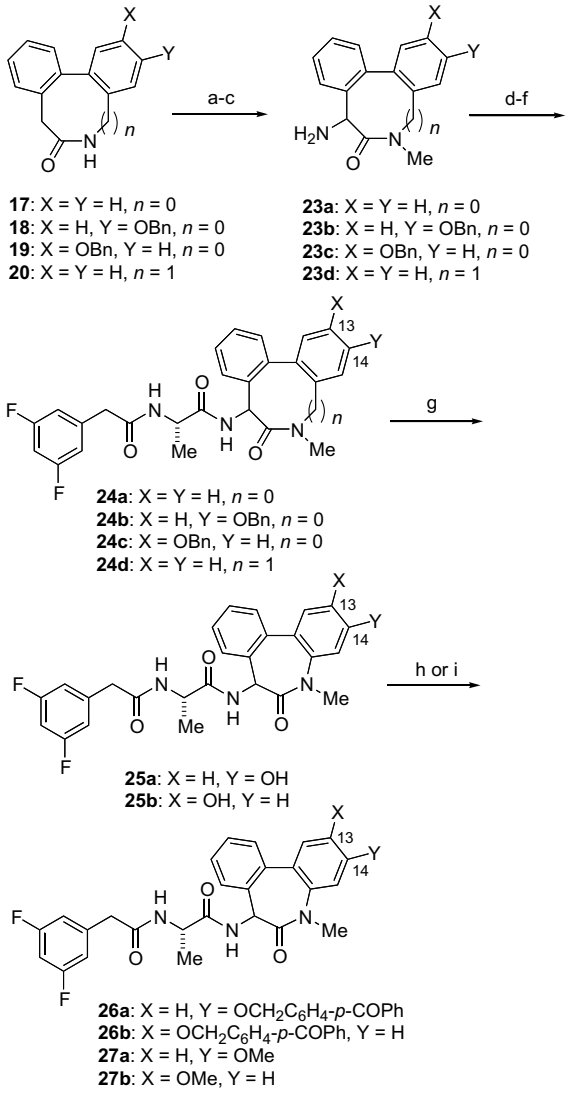
Table 1. Construction of medium-sized rings via Staudinger–aza-Wittig strategy[a]

Entry	ω-Azido pfp ester	Product	Yield
			
1	**11**: X = H, Y = H	**17**: X = H, Y = H	76
2[b]	**12**: X = H, Y = OBn	**18**: X = H, Y = OBn	81
3[b]	**13**: X = OBn, Y = H	**19**: X = OBn, Y = H	99
4	 **14**	 **20**	93
5	 **15**	 **21**	45
6[c]			82
7[d]	 **16**	 **22**	85

[a] All reactions were performed using *n*-Bu_3P (5 equiv) in toluene (10 mM) at rt unless otherwise noted.
[b] THF (10 mM), rt.
[c] Toluene (10 mM), 100 °C.
[d] Toluene (3 mM), 100 °C.

on our preliminary investigation, we employed *n*-Bu_3P (5 equiv) as a reagent and the reactions were carried out under high-dilution conditions. Cyclization of ω-azido pfp esters (**11**–**14**) proceeded smoothly at room temperature to give the corresponding 7- and 8-membered lactams **17**–**20** in high yields (entries 1–4). On the other hand, formation of much challenging larger 9- and 10-membered lactams called for elevated temperature conditions (toluene, 100 °C) to attain satisfactory yields (entries 5–7).[9]

With various medium-sized lactams in hand, we next focused our attention to the synthesis of LY411575 analogues (Scheme 3). N-methylation of lactams (**17**–**20**) were followed by treatment with KHMDS in the presence of *n*-BuONO, and subsequent reduction of the derived oximes with Zn/TFA[10] afforded amines **23a**–**d**, respectively. Condensation of **23a**–**d** with Boc-protected L-alanine (EDC, HOBt), deprotection of the Boc group, and a second EDC-mediated coupling with 3,5-difluorophenylacetic acid furnished the analogues **24a**,[2b] **24b**–**d** in good yields. Cleavage of the benzyl ether of **24b**,**c** under catalytic transfer hydrogenation conditions[11] furnished phenolic analogues **25a**,**b** without touching aryl fluorines. Alkylation of the liberated phenol with 4-(bromomethyl)benzophenone[12] or CH_3I gave rise to benzophenone analogues **26a**,**b** or methyl ether analogues **27a**,**b**, respectively.



Scheme 3. Reagents and conditions: (a) CH_3I, NaH, DMF, 0 °C → rt; (b) *n*-BuONO, KHMDS, THF, 0 °C; (c) Zn, TFA/CH_2Cl_2 (1:4), rt, 90% (**23a**), 86% (**23b**), 88% (**23c**), 77% (**23d**) for three steps; (d) Boc-L-Ala, EDC, HOBt, NMM, THF, 0 °C → rt; (e) TFA, CH_2Cl_2, rt; (f) 3,5-Difluorophenylacetic acid, EDC, HOBt, NMM, THF, 0 °C → rt, 83% (**24a**), 86% (**24b**), 83% (**24c**), 80% (**24d**) for three steps; (g) 20% $Pd(OH)_2$/C, cyclohexene/EtOH (1:2), reflux, quant (**25a**), quant (**25b**); (h) 4-(Bromomethyl)benzophenone, K_2CO_3, DMF, 60 °C, 84% (**26a**), quant (**26b**); (i) CH_3I, K_2CO_3, DMF, 60 °C, 73% (**27a**), 62% (**27b**).

The ability of analogues **24**–**27** to inhibit Aβ formation was evaluated by in vitro assay using recombinant C-terminal fragment of APP as a substrate (Table 2).[13,14] Analogues **24a**,**b** showed excellent inhibitory activity for Aβ40 and Aβ42 productions at low concentrations, while analogue **24c**, in which the benzyloxy group was attached at the C13 position,[15] displayed Aβ40 production inhibition to a lower extent (ca. 5-fold lower than that of **24a**). Ring-expanded analogue **24d** was found to be approximately 42-fold less active for Aβ40 inhibition, suggesting the importance of the ring size of the dibenzolactam moiety. Phenolic analogues **25a**,**b** showed potent activity. Interestingly, production of both Aβ40 and Aβ42 peptides were inhibited at almost same concentrations. Although incorporation of a bulky benzophenonemethyl (*p*-benzoylbenzyl) group at the C14 position was tolerated as analogue **26a** retained potency, analogue **26b** suffered a decrease in its potency (ca. 47-fold less active for Aβ40 inhibition). However, both methyl ether analogues **27a**,**b** retained potent activity. Based on these results, it can be concluded that the incorporation of a substituent at the C14 position is well tolerated but the modification of the C13 is limited to a certain extent.

Table 2. Inhibition of Aβ40 and Aβ42 productions by LY411575 analogues in vitro

Compound	IC_{50} (nM)	
	Aβ40	Aβ42
24a	5.2	14
24b	7.5	50
24c	28	28
24d	217	381
25a	14	15
25b	20	20
26a	37	51
26b	246	218
27a	18	20
27b	27	42

As demonstrated in the synthesis of analogues **26**–**27**, it is worthy to note that diverse alkyl groups could be selectively attached to the phenol group within analogues **25a**,**b**. Furthermore, in principle, use of CT_3I instead of CH_3I in this alkylation process could furnish potent radioligands (CT_3)-**27a**,**b**. Thus, although phenolic analogues **25a**,**b** themselves are potent γ-secretase inhibitors, they are also expected to serve as promising precursors for further elaboration of structural variants and for the generation of photoaffinity probes[16] and radioligands, useful for biological studies on γ-secretase.

In summary, an intramolecular Staudinger–aza-Wittig reaction of ω-azido pfp ester has successfully been applied to the construction of 7–10 membered lactams, demonstrating the generality and efficiency of the present tactic for the synthesis of medium-sized lactams. Its application to the synthesis of LY411575 analogues has also been performed, leading to the generation of new γ-secretase inhibitors. According to the present SAR studies, efforts toward design and synthesis of photoaffinity probes based on **1** and their application to biochemical studies on γ-secretase are currently underway in our laboratories and will be reported in due course.

Acknowledgements

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References and notes

1. For recent reviews see: (a) Schmidt, B. *Chem. Bio. Chem.* **2003**, *4*, 366; (b) Wolfe, M. S.; Haass, C. *J. Biol. Chem.* **2001**, *276*, 5413; (c) Steiner, H.; Haass, C. *Nat. Rev. Mol. Cell Biol.* **2000**, *1*, 217; (d) Sisodia, S. S.; Annaert, W.; Kim, S.-H.; De Strooper, B. *Trends Neurosci.* **2001**, *24*, 52; (e) Tsai, J.-Y.; Wolfe, M. S.; Xia, W. *Curr. Med. Chem.* **2002**, *9*, 1087; (f) Ghosh, A. K.; Hong, L.; Tang, J. *Curr. Med. Chem.* **2002**, *9*, 1135; (g) Wolfe, M. S. *J. Med. Chem.* **2001**, *44*, 2039.
2. (a) Lewis, H. D.; Perez Revuelta, B. I.; Nadin, A.; Neduvelil, J. G.; Harrison, T.; Pollack, S. J.; Shearman, M. S. *Biochemistry* **2003**, *42*, 7580; (b) Wu, J.; Tung, J. S.; Thorsett, E. D.; Pleiss, M. A.; Nissen, J. S.; Neitz, J.; Latimer, L. H.; John, V.; Freedman, S.; Britton, T. C.; Audia, J. E.; Reel, J. K.; Mabry, T. E.; Dressman, B. A.; Cwi, C. L.; Droste, J. J.; Henry, S. S.; McDaniel, S. L.; Scott, W. L.; Stucky, R. D.; Porter, W. J. *PCT Int. Appl.*, WO9828268.
3. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635; (b) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
4. (a) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; (b) Eguchi, E.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced.* **1992**, *24*, 209.
5. Very recently van Maarseveen and co-workers have reported an intramolecular Staudinger ligation method for the construction of medium-sized lactams. See: David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed* **2003**, *42*, 4373.
6. Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112.
7. (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
8. (a) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517; (b) Baudoin, O.; Cesario, M.; Guénard, D.; Guritte, F. *J. Org. Chem.* **2002**, *67*, 1199; (c) Baudoin, O.; Guénard, D.; Guritte, F. *J. Org. Chem.* **2000**, *65*, 9268.
9. In contrast to our previous result (Ref. 6) all medium-sized lactams synthesized in the present study (**17**–**22**) could be directly isolated without conducting hydrolysis separately.
10. We have found that use of trifuluoroacetic acid (TFA) as a co-solvent was crucial for clean reduction of oximes. For a related example see: Negi, S.; Matsukura, M.; Mizuno, M.; Miyake, K.; Minami, N. *Synthesis* **1996**, 991.
11. Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396.
12. (a) Patricelli, M. P.; Cravatt, B. F. *Biochemistry* **2001**, *40*, 6107; (b) Tamiaki, H.; Kiyomori, A.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1768.
13. (a) Takahashi, Y.; Hayashi, I.; Tominari, Y.; Rikimaru, K.; Morohashi, Y.; Kan, T.; Natsugari, H.; Fukuyama, T.; Tomita, T.; Iwatsubo, T. *J. Biol. Chem.* **2003**, *278*, 18664; (b) Takasugi, N.; Tomita, T.; Hayashi, I.; Tsuruoka, M.; Niimura, M.; Thinakaran, G.; Takahashi, Y.; Iwatsubo, T. *Nature* **2003**, *422*, 438.
14. Each analogue was synthesized as a 1:1 mixture of diastereomers and used in the assay without separation.
15. The carbon numbering in this paper is according to Ref. 2b.
16. Kan, T.; Tominari, Y.; Morohashi, Y.; Natsugari, H.; Tomita, T.; Iwatsubo, T.; Fukuyama, T. *Chem. Commun.* **2003**, 2244.