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Total synthesis of (−)-aplaminal by Buchwald–Hartwig cross-coupling of an aminal†

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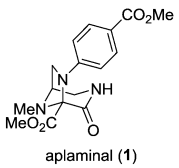
The concise total synthesis of an unusual alkaloid, aplaminal, has been accomplished. The synthetic feature is the Buchwald–Hartwig cross-coupling between a novel triazabicyclo[3.2.1]octane core and an aromatic bromide. The practicality of our approach provides aplaminal analogs and preliminary structure–cytotoxicity relationships of an aromatic moiety were achieved.

Natural product synthesis and synthetic methodology may produce synergistic effects with each other. When a chemical reaction is developed, chemists study the synthesis of useful compounds by using the reaction and improve it by clarifying its scope and limitations by optimizing the reaction conditions. For example, cross-coupling reactions are used not only in natural product synthesis but also in a wide range of fields such as bioconjugations, material sciences, and process chemistry.[1] Among them, the Buchwald–Hartwig coupling reaction[2] is used in many syntheses involving nitrogen nucleophiles as one of the coupling partners and their application range is wide. Many ligands for this reaction have been developed.[3]

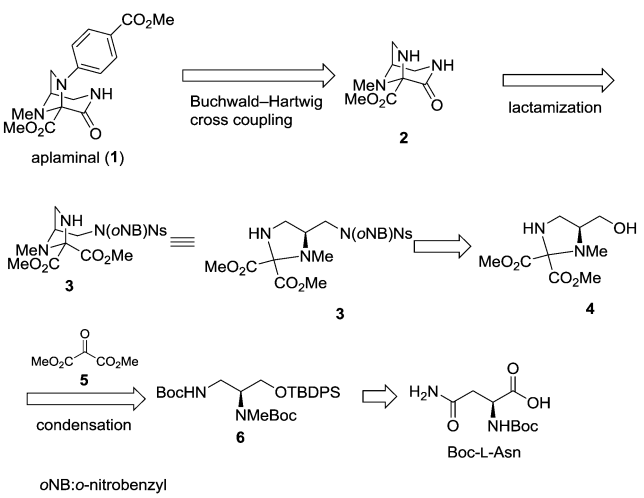
Aplaminal (**1**), isolated from the Japanese sea hare *Aplysia kurodai* by our group in 2008, has an unusual triazabicyclo-[3.2.1]octane skeleton (Fig. 1).[4] Owing to its unique structural feature, aplaminal (**1**) has attracted the attention of synthetic organic chemists. Smith and co-worker achieved the first elegant total synthesis and assignment of the absolute configuration of aplaminal.[5] However, the previous biological study on aplaminal (**1**) was limited to its cytotoxicity against HeLa S3 cells.[4] Therefore, we started to develop an adaptable and a scalable synthetic route of aplaminal (**1**) for a structure–activity relationships study and chemical probe development. By focusing on the aromatic ring of aplaminal (**1**), we envisioned the introduction of an aryl moiety *via* a cross-coupling reaction at a late stage of the synthesis for the structure–activity relationships study. Although Buchwald–Hartwig cross coupling involves amides or amines, there have been no reports on the use of an aliphatic aminal to date.[6] Therefore, we decided to establish the adaptable synthetic route of **1** by using the Buchwald–Hartwig cross-coupling reaction of an aliphatic aminal as a key step.



aplaminal (**1**)

Fig. 1 Structure of aplaminal (**1**).

The retrosynthetic pathway of aplaminal (**1**) is shown in Scheme 1. Aplaminal (**1**) was synthesized by a Buchwald–Hartwig cross-coupling of the bicyclic core **2** and an aromatic halide. This plan would be suitable for the synthesis of its analogs.



Scheme 1 Retrosynthetic pathway of aplaminal (**1**).

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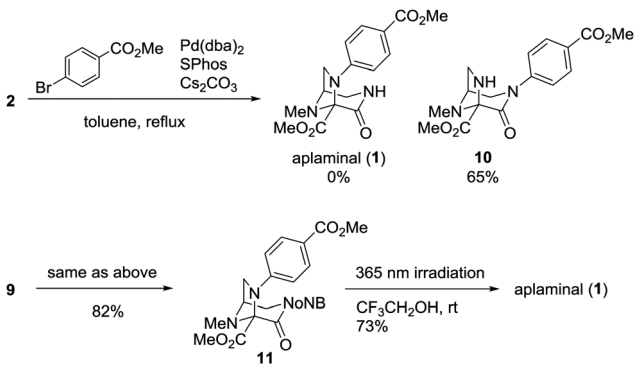
Compound **2** was conveniently assembled from amine **3** by lactamization. Because Smith reported that the hydrogenation of a benzyl group could not succeed in the presence of an aminal moiety,[5] we decided to use an *o*-nitrobenzyl (*o*NB) group as the protecting group on the amino functionality. The third nitrogen functional group was introduced in aminal **4** by a Mitsunobu reaction. Aminal **4** was then constructed by condensation between diamine **6** and dimethyl 2-oxomalonate (**5**). Diamine **6** was synthesized from commercially available Boc-L-Asn.

The starting point for this work was the synthesis of bicyclic core **2** (Scheme 2). The known Boc-L-Dap-OH was synthesized from Boc-L-Asn by a Hofmann rearrangement.[7] Borane reduction of the carboxylic acid moiety to a hydroxy group and the Boc group to a methyl group followed by Boc protection of both amino groups gave alcohol **7**. Aminal **8** was obtained from alcohol **7** by a sequence of reactions: protection of the primary hydroxy group, removal of both Boc groups, and condensation with oxo-malonate **5**. Removal of the TBDPS group in **8** afforded the precursor **4** for the Mitsunobu reaction. Next, we attempted the Mitsunobu reaction[8] with *o*-nitrobenzyl nosylamide to give the desired compound **3** in 32% yield. After removal of the Ns group by PhSH, lactamization gave the protected bicyclic core **9**. Removal of the *o*NB group with 365 nm irradiation afforded bicyclic core **2**, one of the desired coupling partners of the Buchwald–Hartwig cross-coupling.

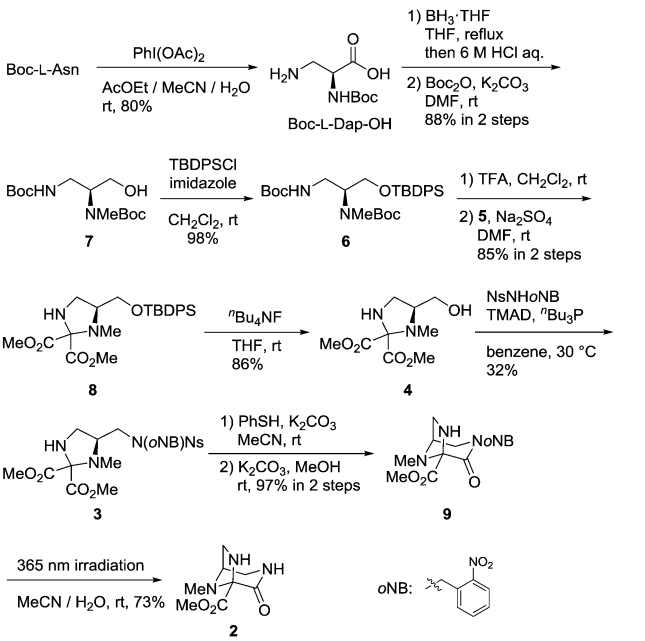
With the coupling partner **2** in hand, we examined the Buchwald–Hartwig cross-coupling reaction (Scheme 3). The Buchwald–Hartwig cross-coupling of **2** was carried out using $Pd(dba)_2$ and SPhos,[9] a widely used phosphine ligand for this reaction. However, aplaminal (**1**) could not be obtained, instead compound **10** in which the reaction proceeded at the amide moiety was obtained. Also, Goldberg amination[10] and Chan–Lam–Evans coupling[11] did not produce aplaminal (**1**). Therefore, we next tried the coupling reaction with **9**, in which the amide moiety was protected. The bicyclic core **9** underwent the Buchwald–Hartwig cross-coupling reaction of the aminal moiety. Finally, removal of the *o*NB group with 365 nm irradiation afforded aplaminal (**1**). The spectroscopic data of the synthesized aplaminal (**1**) were in full agreement with those of the natural sample.[4]

Thus, total synthesis of aplaminal (**1**) was achieved. However, the overall yield was low (9% yield) because of the low-yielding Mitsunobu reaction. Therefore, we reconsidered the synthetic route for compound **3**. We thought that the instability of the aminal moiety caused the low yield of the Mitsunobu reaction. Therefore, the Mitsunobu reaction was performed with compound **7**, but the reaction did not proceed. Alternatively, we tried to introduce a nitrogen function by reductive amination (Scheme 4). Dess–Martin oxidation of alcohol **7** followed by reductive amination of the resultant aldehyde with oNBNH$_2$ gave amine **12**. After protection of the amino group, removal of both the Boc groups and condensation with oxo-malonate **5** gave aminal **3**. In this way, the net yield for the conversion of alcohol **7** to aminal **3** could be improved about three times over that of the Mitsunobu reaction route, and the overall yield of aplaminal (**1**) was also significantly improved to 33%.

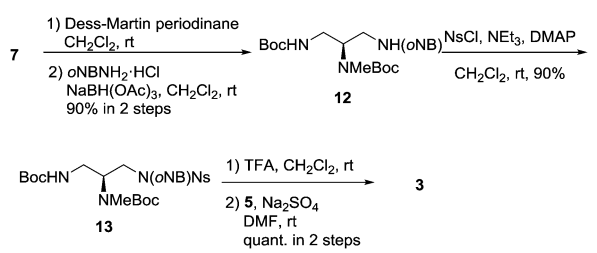
Thus, since the optimal synthetic route for a structure–activity relationship was established, several analogs were synthesized (Table 1). Interestingly, the coupling reaction proceeded with aryl halides having an electron withdrawing group (entries 1, 2, 4, and 5), but the reaction did not occur with aryl halides having electron donating groups (entries 7 and 8) or fluorine (entry 6). Even with a carbomethoxy group, the ortho compound failed in the reaction perhaps because of steric hindrance (entry 3). Although various



Scheme 3 Total synthesis of aplaminal (**1**).

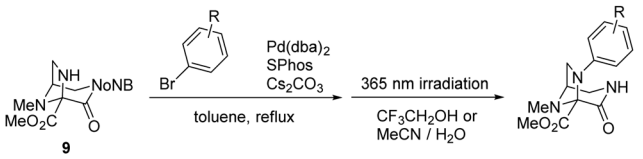


Scheme 2 Synthesis of bicyclic core **2**, a coupling partner of Buchwald–Hartwig cross-coupling.



Scheme 4 Improved synthesis of aminal **3**.

Table 1 Syntheses of aplaminal analogs



Entry	R	Yield (2 steps) (%)	Product
1[a]	*p*-CO_2Me	60	Aplaminal (**1**)
2[b]	*m*-CO_2Me	13	**14**
3	*o*-CO_2Me	0	**15**
4[b]	*p*-Cl	6	**16**
5[b]	*p*-CN	3	**17**
6	*p*-F	0	**18**
7	*p*-OMe	0	**19**
8	*p*-Me	0	**20**
9[c]	H	0	**21**

[a] CF_3CH_2OH was used. [b] MeCN/H_2O was used. [c] PhBr and PhI were used, respectively.

Table 2 Cytotoxicity of aplaminal (**1**) and its analogs

Compound	Cytotoxicity against HeLa S3 cells IC_{50} values (μM)
1 (natural)	29
1 (synthetic)	23
2	>1000
10	>1000
14	>1000
16	>1000
17	72

conditions such as ligands, bases, and solvent were examined using bromobenzene or iodobenzene, the reaction still did not proceed (entry 9).[12]

Cytotoxicity against HeLa S3 cells of aplaminal (**1**) and its analogs was evaluated (Table 2). As a result, synthetic aplaminal (**1**) showed moderate cytotoxicity as did the natural sample. On the other hand, compounds **2** and **10** showed no cytotoxicity, revealing that an aromatic ring on the aminal nitrogen atom is important for cytotoxicity. Also, the *m*-carbomethoxy analog **14** and chloro analog **16** showed no cytotoxicity. On the other hand, nitrile analog **17** exhibited a slightly weaker cytotoxicity than **1**. From these results, analogs with a strong electron withdrawing group at the para position show cytotoxicity, thus supposing that the nature and position of the substituent on the benzene moiety is important for the interaction with the target protein.

Conclusions

We have accomplished a concise total synthesis of aplaminal (**1**). A key step in the synthesis was the Buchwald–Hartwig cross-coupling involving an aliphatic aminal and an aromatic bromide. Furthermore, we synthesized aplaminal analogs and investigated their cytotoxicity, revealing that an electron withdrawing group at the para position of the phenyl group is essential for the cytotoxicity. A detailed structure–activity relationship study based on this synthetic strategy is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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12 We tried XPhos, DavePhos, JohnPhos, and BINAP as ligands, *t*BuOK as a base, and DMF and xylene as solvents, and under microwave condition. However, coupling product could not be obtained.

