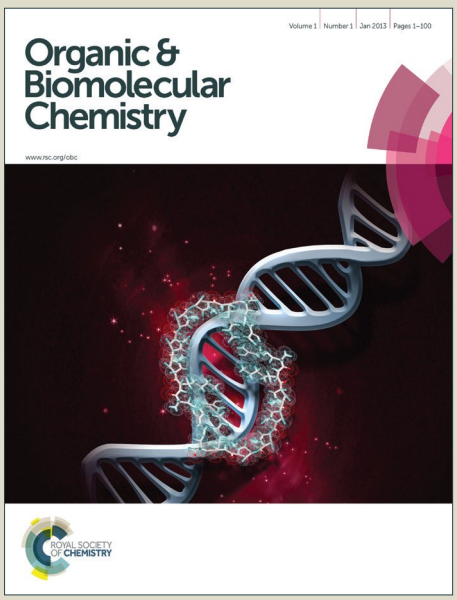
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

DMSO/Tf_2O-Mediated Cross-Coupling of Tryptamine with Substituted Aniline to Access C3a-N1′-Linked Pyrroloindoline Alkaloids

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Masanori Tayu, Takako Ishizaki, Kazuhiro Higuchi*, and Tomomi Kawasaki*

The cross-coupling of tryptamine with aniline to C3a-nitrogen-linked pyrroloindoline has been developed via the consecutive cyclization of tryptamine with DMSO/Tf_2O and substitution of 3a-pyrroloindolylthionium intermediate with aniline. The use of 2,3-dihydrotryptamine instead of aniline enabled easy access to 3a-(1-indolyl)pyrroloindoline and the concise synthesis of C3a-N1′-linked pyrroloindoline alkaloid (±)-psychotriasine was accomplished.

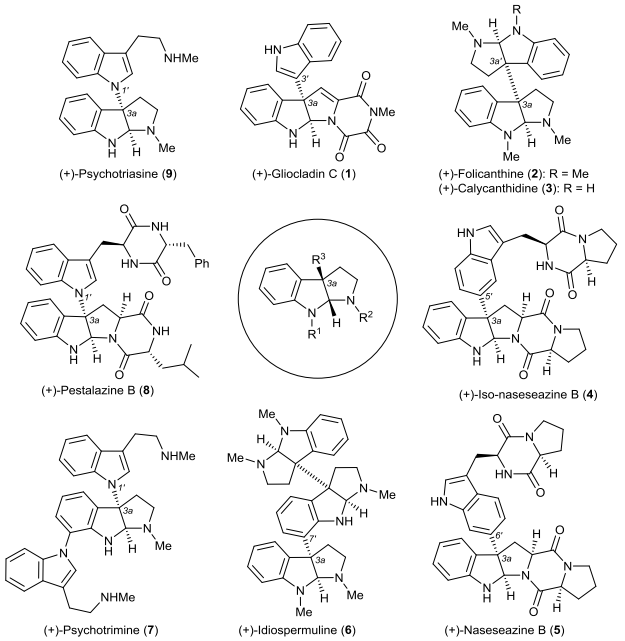


Fig. 1 Represented 3a-indolylpyrroloindoline alkaloids.

Pyrroloindoline alkaloids are a biologically important class of natural products.[1)] Most of these alkaloids are linked to an indolyl moiety at the C3a-position through a carbon-carbon connection such as gliocladin C (**1**, C3a-C3′),[2)] folicanthine (**2**, C3a-C3a′),[3)] calycanthidine (**3**, C3a-C3a′),[4)] iso-naseseazine B (**4**, C3a-C5′),[5)] naseseazine B (**5**, C3a-C6′),[5)] or idiospermuline (**6**, C3a-C7′)[6)] (Figure 1). Recently, the 3a-(1-indolyl)pyrroloindoline motif, which is an unusual C3a-N1′ linkage, has been found in several alkaloids, including psychotrimine (**7**),[7)] pestalazine B (**8**),[8)] and psychotriasine (**9**).[9)] The construction of this motif is an attractive research area because of the intriguing structures and biological activities of these alkaloids.[10)] Several synthetic methods for the 3a-nitrogen-substituted pyrroloindoline have been developed;[11-14)] however, there are only a few reactions for constructing the C3a-N1′-linked framework concisely. For example, the substitution of 3a-bromopyrroloindoline with indole[11a)] and the oxidative coupling of tryptamine with *o*-iodoaniline, followed by the transformation to the indole moiety.[12a)] Nevertheless, the effective construction of the C3a-N1′ linkage between the pyrroloindoline and indole cores has remained a challenge.

Scheme 2 Our previous and present works.

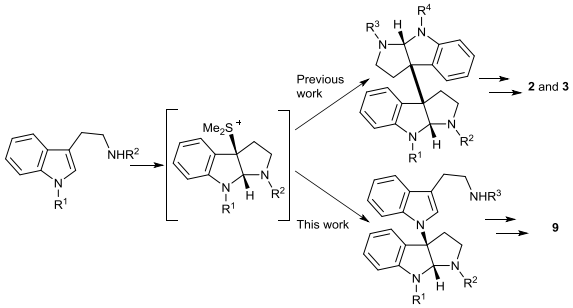
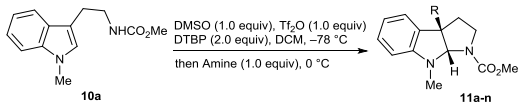
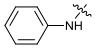
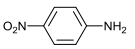
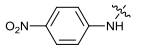
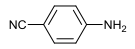
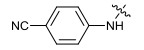
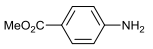
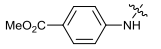
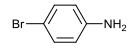
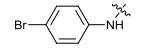
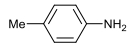
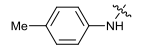
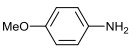
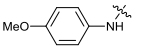
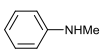
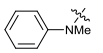
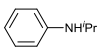
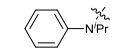
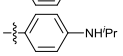
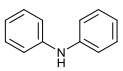
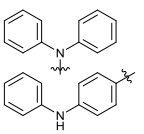
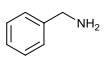
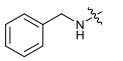
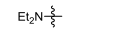


Table 1 Investigation of aniline nucleophiles for synthesizing 3a-nitrogen-substituted pyrroloindoline.



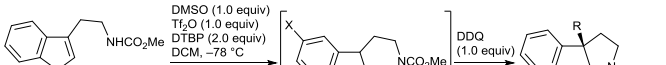
Entry	Amine	R	11	Yield (%)
1			11a	91
2			11b	90
3			11c	96
4			11d	93
5			11e	89
6			11f	74
7			11g	38
8			11h	83
9			11i	33
			11j	40
10			11k	76
			11l	6
11			11m	30
12	Et_2NH		11n	9

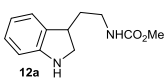
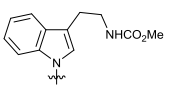
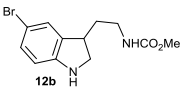
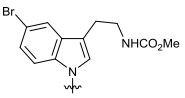
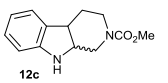
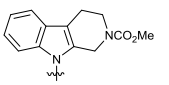
In investigating DMSO/Tf_2O-mediated reactions, we have recently developed a concise method for constructing the C3a-C3a′ coupled bispyrroloindoline framework in 2 and 3 (Scheme 1).[15] Because the DMSO/Tf_2O-mediated reaction formed a regioselective C3a-C3′ linkage even with *N*-unsubstituted indoles, we then used aniline and indoline derivatives as *N*-nucleophiles to form the C3a-N1′ linkage in **7**–**9**. Herein, we report the DMSO/Tf_2O-mediated reaction to provide a convenient method for constructing the C3a-N1′ linkage, and the short-step synthesis of (±)-psychotriasine (**9**)[9] from 2,3-dihydrotryptamine.

For the synthesis of 3a-nitrogen-substituted pyrroloindoline **11** from tryptamine **10a**, we initially explored the use of aniline as an *N*-nucleophile (Table 1). Tryptamine **10a** was treated with DMSO, Tf_2O, and 2,6-di-*tert*-butylpyridine (DTBP) at –78 °C for 10 min. Successively, the generated intermediate was allowed to react with aniline at 0 °C for 10 min to afford desired 3a-anilinopyrroloindoline **11a** in 91% yield (entry 1). In the case of *p*-nitroaniline, the same reaction proceeded smoothly to form desired amino product **11b** in 90% yield (entry 2). Similarly, *p*-cyano-, *p*-methoxycarbonyl-, and *p*-bromoanilines that bear an electron-withdrawing group also provided corresponding products **11c**–**e** in excellent yields (entries 3–5). In contrast, the reaction of *p*-toluidine and *p*-anisidine with electron-donating groups decreased the yield of **11f** and **11g** (entries 6 and 7). As shown in entry 8, *N*-methylaniline reacted smoothly to afford 3a-nitrogen-substituted product **11h** in 83% yield. *N*-Isopropylaniline furnished desired 3a-nitrogen product **11i** (33%) with the formation of C3a-C4′-linked **11j** (40%) (entry 9). The use of diphenylamine provided **11k** preferentially in 76% yield with **11l** in 6% yield (entry 10). The reaction with alkylamines such as benzylamine and diethylamine provided corresponding amino products **11m** and **11n**, respectively, in low yields from a complicated reaction mixture (entries 11 and 12). These results indicated that the suitable basicity and smallness of *N*-nucleophiles were important for constructing the C3a-N linkage.

We envisioned that, as with aniline, 2,3-dihydrotryptamine would lead to construct C3a-N1′ linkage for alkaloids **7**–**9** (Table 2). When 2,3-dihydrotryptamine **12a**[16a] was utilized used in the reaction of **10a**, expected 1-indolinyl product **13** was too labile to handle easily. Subsequent DDQ oxidation converted **13** to stable 1-indolyl product **11o** (47%) and an inseparable mixture (entry 1). On using 5-bromo-2,3-dihydrotryptamine **12b**[16b] to avoid undesired reactions, **11p** was obtained in 91% (entry 2). Moreover, the reaction with hexahydro-β-carboline **12c**[16c] followed by DDQ oxidation also produced C3a-N1′-linked product **11q** in 60% yield.

Table 2 Concise construction of 3a-(1-indolyl)pyrroloindoline framework.

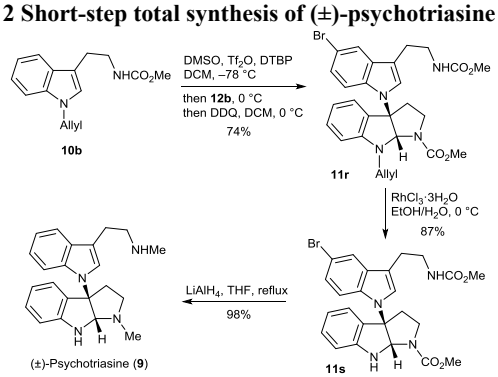


Entry	12	R	11	Yield[a] (%)
1			11o	47
2			11p	91
3			11q	60

[a] The yield after DDQ oxidation.

We applied this reaction in a concise synthesis of (±)-psychotriasine (**9**)[9] which has a C3a-N1′ linkage between two tryptamines. The coupling reaction of *N*a-allyltryptamine **10b** with 2,3-dihydrotryptamine **12b** and the following DDQ oxidation gave desired 3a-(1-indolyl)pyrroloindoline **11r** in 74% yield. Next, deallylation with $RhCl_3•3H_2O$ followed by $LiAlH_4$ reduction of the methoxycarbonyl groups and debromination afforded (±)-psychotriasine (**9**). The spectral data for synthetic product **9** were identical to those of the natural product.[9a]

Scheme 2 Short-step total synthesis of (±)-psychotriasine (9).



Conclusions

We have established a DMSO/Tf_2O-mediated cross-coupling of tryptamine with aniline derivatives to synthesize 3a-nitrogen-substituted pyrroloindolines. The utility of this reaction was demonstrated through concise access to C3a-N1′-linked bistryptamines, including (±)-psychotriasine (**9**), which were successfully synthesized by the use of 2,3-dihydrotryptamines **12**. We are currently developing the enantioselective reaction and applying it to the asymmetric syntheses of psychotrimine (**7**) and pestalazine B (**8**).

Acknowledgements

We gratefully acknowledge financial support from JSPS KAKENHI Grant Number 25860014. We also thank N. Eguchi, T. Koseki, and S. Yamada at the Analytical Center of our university for performing microanalysis, NMR and mass spectrometry measurements.

Notes and references

Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

1 (a) G. A. Cordell, J. E. Saxton, in *The Alkaloids: Chemistry and Physiology*, ed. R. H. F. Manske, and R. G. A. Rodrigo, Academic Press, New York, 1981, vol. 20, ch. 1, p. 1; (b) T. Hino, M. Nakagawa, in *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic Press, San Diego, 1988, vol. 34, ch. 1, p. 1; (c) U. Anthoni, C. Christophersen, P. H. Nielsen, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon, Amsterdam, 1999, vol. 13, ch. 2, p. 163; (d) T.-S. Kam, Y.-M. Choo, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Academic Press, 2006, vol 63, ch. 4, p. 181; (e) A. Steven, L. E. Overman, *Angew. Chem., Int. Ed*., 2007, **46**, 5488; (f) M. A. Schmidt, M. Movassaghi, *Synlett*, 2008, 313; (g) P. Ruiz-Sanchis, S. A. Savina; F. Albericio, M. Álvarez, *Chem. Eur. J.*, 2011, **17**, 1388; (h) S. Tadano, H. Ishikawa, *Synlett*, 2014, 157.

2 Y. Usami, J. Yamaguchi, A. Numata, *Heterocycles*, 2004, **63**, 1123.

3 (a) K. Eiter, O. Svierak, *Monatsh. Chem*., 1951, **82**, 186; b) K. Eiter, O. Svierak, *Monatsh. Chem.*, 1952, **83**, 1453.

4 (a) G. Barger, A. Jacob, J. Madinaveitia, *Recl. Trav. Chim*., 1938, **57**, 548; (b) J. E. Saxton, W. G. Bardsley, G. F. Smith, *Proc. Chem. Soc.*, 1962, 148.

5 (a) R. Raju, A. M. Piggott, M. Conte, W. G. L. Aalbersberg, K. Feussner, R. J. Capon, *Org. Lett*., 2009, **11**, 3862; structure revision, (b) J. Kim, M. Movassaghi, *J. Am. Chem. Soc*., 2011, **133**, 14940.

6 R. K. Duke, R. D. Allan, G. A. R. Johnston, K. N. Mewett, A. D. Mitrovic, C. C. Duke, T. W. Hambley, *J. Nat. Prod.*, 1995, **58**, 1200.

7 H. Takayama, I. Mori, M. Kitajima, N. Aimi, N. H. Lajis, *Org. Lett*., 2004, **6**, 2945.

8 (a) G. Ding, L. Jiang, L. Guo, X. Chen, H. Zhang and Y. Che, *J. Nat. Prod*., 2008, **71**, 1861; structure revision, (b) C. Pérez-Balado, Á. R. de Lera, *Org. Biomol. Chem.*, 2010, **8**, 5179.

9 (a) H. Zhou, H.-P. He, Y.-H. Wang, X.-J. Hao, *Helv. Chim. Acta*, 2010, **93**, 1650; synthesis, (b) T. Newhouse, C. A. Lewis, K. J. Eastman, P. S. Baran, *J. Am. Chem. Soc*., 2010, **132**, 7119.

10 (a) Antitumor activity: N. Takahashi, T. Ito, Y. Matsuda, N. Kogure, M. Kitajima, H. Takayama, *Chem. Commun*., 2010, **46**, 2501; (b) antibacterial activity: M. A. Schallenberger, T. Newhouse, P. S. Baran, F. E. Romesberg, *J. Antibiot.*, 2010, **63**, 685; (c) cytotoxicity: G. Ding, L. Jiang, L. Guo, X. Chen, H. Zhang, Y. Che, *J. Nat. Prod*., 2008, **71**, 1861.

11 Substitution of 3a-bromopyrroloindoline with aniline, (a) V. R. Espejo, J. D. Rainier, *J. Am. Chem. Soc*., 2008, **130**, 12894; (b) I. Villanueva-Margalef, D. E. Thurston, G. Zinzalla, *Org. Biomol. Chem*., 2010, **8**, 5294.

12 Oxidative coupling of tryptamine with *o*-iodoaniline, (a) T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 10886; (b) Z.-J. Cai, S.-Y. Wang, S.-J. Ji, *Org. Lett*., 2013, **15**, 5226.

13 Electrophilic cyclization of tryptamine with diazene, Z. Zhang, J. C. Antilla, *Angew. Chem., Int. Ed*., 2012, **51**, 11778.

14 Aziridination-intramolecular cyclization of tryptamine with rhodium nitrene, S. Beaumont, V. Pons, P. Retailleau, R. H. Dodd, P. Dauban, *Angew. Chem., Int. Ed.*, 2010, **49**, 1634.

15 M. Tayu, K. Higuchi, T. Ishizaki, T. Kawasaki, *Org. Lett*., 2014, **16**, 3613.

16 (a) M. Somei, N. Oshikiri, M. Hasegawa, F. Yamada, *Heterocycles*, 1999, **51**, 1237; (b) M. Hasegawa, K. Yamada, Y. Nagahama, M. Somei, *Heterocycles*, 1999, **51**, 2815; (c) M. Somei, *JP Pat*., 08 157 475 1994.