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Synthesis of D-Abrines by Palladium-catalyzed Reaction of ortho-Iodoanilines with *N*-Boc-*N*-methylalanyl-substituted Acetaldehyde and Acetylene

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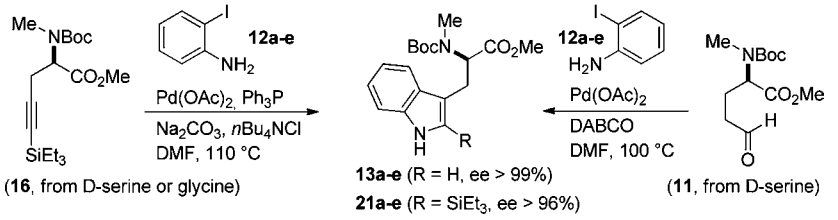
ABSTRACT



A novel strategy to *N*-Boc-*N*-methyl–tryptophans (abrine derivatives) was developed that relies on the palladium-catalyzed annulation of ortho-iodoanilines 12 with either *N*-Boc-*N*-methyl-propargylglycine 16 or aldehyde 11. Both 11 and 16 can be prepared from D-serine. An alternative route to propargylglycine 16 utilizes an enantioselective propargylation reaction of glycine imine 17.

A common feature of post-translationally modified peptides and depsipeptides is the presence of *N*-methylated amino acids. Frequently such amino acids occur in the less commonly encountered D-configuration. This simple modification can influence the conformation, protect the corresponding peptide bond toward attack by proteases and change the hydrogen bonding pattern compared to the nonmethylated analogue. A prominent example is *N*-methyl tryptophan, also called abrine. It can be found in the cyclodepsipeptides jasplakinolide[1] **1** and the chondramides[2] **2**–**5** (Figure 1). These are natural products that target the actin skeleton.

A classical route to *N*-methylamino acids is to start from the amino acid, protect the amino group as a carbamate and then to methylate the dianion, for example with NaH/CH_3I in DMF.[3,4] However in the case of tryptophan this strategy requires protection of the indole NH prior to the *N*-methylation step.[5] The same is true for other side chain functionalized amino acids. An alternative that avoids protection of the indole NH is via sequential reductive amination, first with benzaldehyde then with paraformaldehyde, followed by debenzylation through catalytic hydrogenation and urethane formation.[6] In addition, the reduction of formamide derivatives has been used as a means of *N*-methylation.[7]

In connection with the synthesis of chondramide A analogues, we required several D-abrine derivatives modified in the indole ring. We wondered whether some of the known convergent strategies to tryptophans might be adaptable to

(1) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett*. **1986**, *27*, 2797–2800.

(2) (a) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot*. **1995**, *48*, 1262–1266. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Liebigs Ann*. **1996**, 285–290.

(3) See, for example: (a) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem*. **1977**, *55*, 906–910. (b) Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem*. **2003**, *68*, 2652–2667. (c) Malkov, A. V.; Vranková, K.; Cerný, M.; Kocovský, P. *J. Org. Chem*. **2009**, *74*, 8425–8427.

(4) For a review, see: Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev*. **2004**, *104*, 5823–5846.

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(7) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem*. **1991**, *56*, 5196–5201.

(8) For a review about synthesis of indoles via palladium-catalyzed reactions, see: Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2011**, *111*, PR215–PR283.

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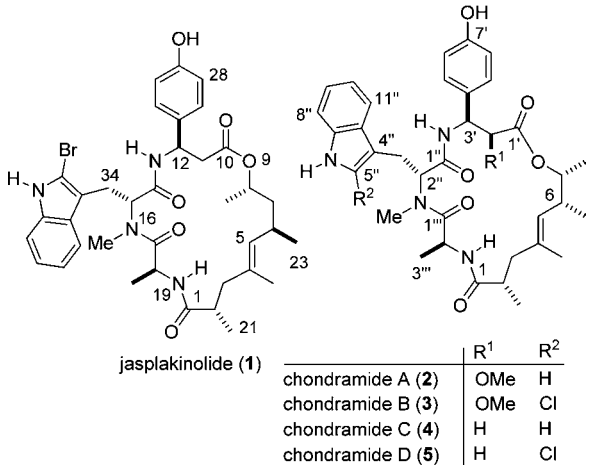


Figure 1. Structures of jasplakinolide (**1**) and the chondramides (**2**–**5**).

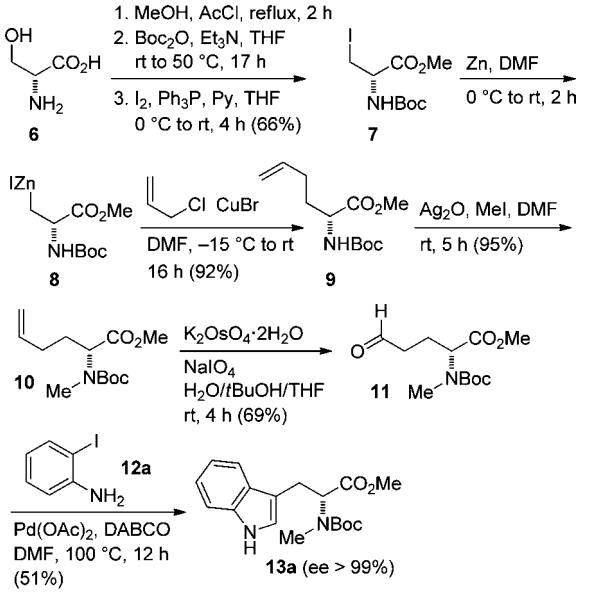
the direct synthesis of abrine derivatives.[8] In this paper we show that this is indeed possible through coupling of ortho-iodoanilines with a functionalized alkyne or aldehyde building block that already contains the *N*-methylated amino acid sector.

One plan was to use the palladium catalyzed annulation between iodoanilines and chiral aldehyde **11**. The group of Zhu has already shown that this indole synthesis, originally developed by Chen,[9] works with *N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentanoate.[10] With a free NH, this reaction proceeded in low yield, probably due to internal hemiaminal formation.

First, homoallyl glycine **9** was prepared from D-serine (**6**), which was converted to *N*-Boc serine methyl ester and from there to iodide **7**, following published procedures.[11] The derived organozinc reagent **8** was then coupled with allyl chloride in presence of copper bromide to give homoallylglycine **9**. For success in this coupling reaction, a solution of iodide **7** should be slowly added to zinc dust, activated by preheating, under a nitrogen atmosphere at 0 °C. After the addition, the cooling bath should be removed and stirring continued for 2 h. After the insertion, the supernatant solution containing the organozinc reagent needs to be added slowly to a solution of copper bromide and allyl chloride in DMF at −15 °C. Thereafter, the mixture is stirred overnight at ambient temperature.

Initially we performed the *N*-methylation of amino acid **9** with NaH/CH_3I in DMF. However, as it turned out, these conditions led to partial racemization (roughly 3:1 ratio of the enantiomers). Better results were obtained with the reagent combination Ag_2O/CH_3I in DMF.[4] For

Scheme 1. Synthesis of Methyl 5-Oxopentanoate **11** and its Coupling with Iodoaniline **12a** to Give D-Abrine **13a**



the *N*-methylation an excess of both silver(I) oxide (4 equiv) and methyl iodide (16 equiv) were used. Under these conditions, *N*-Boc-*N*-methyl homoallylglycine methyl ester **10** was obtained in 95% yield, essentially without any racemization.[12] Subsequent dihydroxylation of the double bond followed by oxidative cleavage of the diol furnished aldehyde **11** in reasonable yield.[13]

The crucial domino sequence consisting of enamine formation between iodoaniline **12a** (1.3 equiv) and aldehyde **11** (1 equiv), followed by Heck cyclization, was performed using the optimized conditions [$Pd(OAc)_2$, DABCO, DMF, 100 °C] of Zhu.[9] In this way, D-abrine **13a** was obtained in 51% yield. The optical purity of **13a** was checked by chiral HPLC, which indicated an ee of >99% (Scheme 1).

On the basis of these results, several other D-abrines were prepared from iodoanilines **12b**–**e** and aldehyde **11** (Table 1). The chemical yields for these coupling reactions were in the range of 38–51%. While occurring with moderate yields, this coupling method provides direct access to the final *N*-methylated tryptophan analogues **13**. The optical purity was determined by chiral HPLC for tryptophan **13a**, which turned out to be very high. This indicated that the coupling conditions did not cause racemization of the chiral center.

Another strategy to convert ortho-iodoanilines to indoles relies on the so-called Larock coupling where disubstituted alkynes are used for a palladium-catalyzed annulation

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(12) The optical purity of amino acid derivative **10** was assessed by chiral HPLC after cleavage of the Boc group and conversion of the amine to the corresponding 2,4,6-trichlorobenzamide derivative, see Supporting Information.

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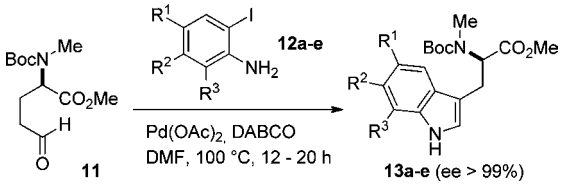
Table 1. Synthesis of Various *N*-Methyl-D-tryptophans by Coupling between Aldehyde **11** and Iodoanilines **12a**–**e**[a]

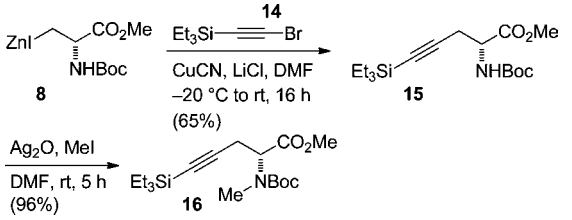


entry	R^1	R^2	R^3	**12**, **13**	yield of **13** (%)
1	H	H	H	**a**	51
2	H	CO_2Me	H	**b**	54
3	H	Cl	H	**c**	47
4	Me	H	Me	**d**	43
5	H	OMe	H	**e**	38

[a] Reaction conditions: $Pd(OAc)_2$ (13 mol %), DABCO (3 equiv), aldehyde **11** (1 equiv), iodoaniline **12** (1.3 equiv), DMF, 100 °C, 12–20 h. The ee-value for **13a** was better than 99%.

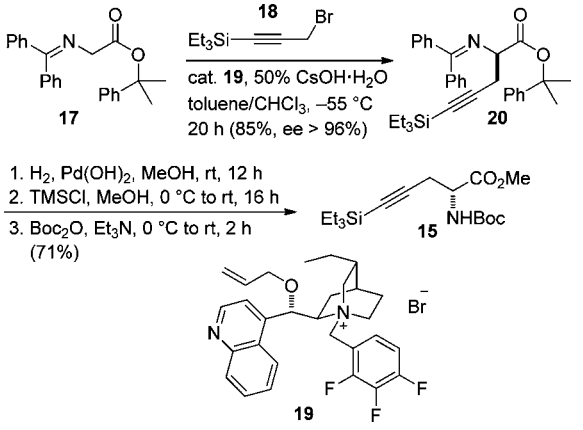
reaction.[14] A corresponding substrate, propargyl glycine **16**, which also should lead directly to *N*-methyl-D-tryptophans, was prepared by two different routes. In route one, compound **15** was synthesized from iodide **7** by the aforementioned Jackson zinc insertion protocol followed by coupling of the organozinc intermediate **8** with 1-bromo-2-triethylsilylacetylene[15] (**14**) (Scheme 2).[16] After reaction of *N*-Boc-alanine derivative **15** with iodomethane and silver(I) oxide, compound **16** was obtained in 96% yield.

Scheme 2. Synthesis of Propargyl Glycine **16** from Iodoalanine **7**



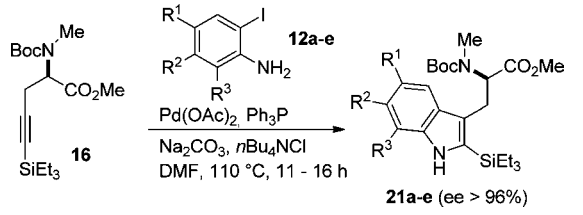
In the second route, the functionalized alkyne **15** was prepared by enantioselective alkylation of cumyl ester protected glycine imine **17** and propargyl bromide[17] **18**, in the presence of phase transfer catalyst **19** (ee = 96%) (Scheme 3).[18] Then, hydrolysis of the imine function and cleavage of the cumyl ester was done by hydrogenolysis in methanol, while maintaining the acid labile acetylene protecting group (TES). After removal of both protecting groups, formation of the methyl ester with TMSCl in methanol[19] followed by protection of the amino group gave propargyl glycine **15** in an overall yield of 71% (3 steps). Initially we used a *tert*-butyl ester group in glycine imine **17**,[20] but the deprotection with TMSCl took 3 d and was accompanied by partial cleavage of the TES.

Scheme 3. Synthesis of Propargyl Glycine **15** by Enantioselective Propargylation of Glycine Imine **17** in the Presence of Chiral Ammonium Salt **19**



With propargyl glycine **16** in hand, the palladium-catalyzed coupling with ortho-iodoanilines **12** using the Larock protocol[13] gave D-abrines **21a**–**e** in 67–95% yield. The obtained ee values were generally larger than 96% (Table 2). Again, the ee-value was determined for the parent compound **21a**, indicating a high ee of 96%.

Table 2. Synthesis of Various *N*-Methyl-D-tryptophans by Coupling between Alkyne **16** and Iodoanilines **12a**–**e**[a]



entry	R^1	R^2	R^3	**12**, **21**	yield of **21** (%)
1	H	H	H	**a**	78
2	H	CO_2Me	H	**b**	67
3	H	Cl	H	**c**	78
4	Me	H	Me	**d**	95
5	H	OMe	H	**e**	82

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol %), Ph_3P (0.1 equiv), Na_2CO_3 (3 equiv), *n*-Bu_4NCl (1 equiv), iodoaniline **12** (1 equiv), alkyne **16** (0.83 equiv), DMF, 110 °C, 11–16 h. The ee-value for **21a** was better than 96%.

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In summary, we have described the direct synthesis of a variety of known and novel *N*-Boc-*N*-methyl-tryptophans by palladium-catalyzed annulation of ortho-iodoanilines **12** with either (*R*)-methyl 2-((*tert*-butoxycarbonyl)(methyl)-amino)-5-oxopentanoate (**11**) or (*R*)-methyl 2-((*tert*-butoxy-carbonyl)(methyl)amino)-5-(triethylsilyl)pent-4-ynoate (**16**). The yields for the annulation step were generally higher using the Larock variant. These abrines should be useful for incorporation into peptides and depsipeptides.

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Supporting Information Available. Experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.