EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Two-step Catalytic Transformation of N-Benzyllactams to Alkaloids (±)-Solenopsin, (±)-Solenopsin A, and (+)-Julifloridine

Authors: Wei Ou, Guang-Sheng Lu, Dong An, Feng Han, and Pei-Qiang Huang

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901752

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901752

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201901752

COMMUNICATION

WILEY-VCH

Two-step Catalytic Transformation of *N*-Benzyllactams to Alkaloids (±)-Solenopsin, (±)-Solenopsin A, and (+)-Julifloridine

Wei Ou,[a,b][‡] Guang-Sheng Lu,[a][‡] Dong An,[a] Feng Han,[a] and Pei-Qiang Huang*[a]

Dedicated to the memory of the late Professor Michel Che for his contribution to catalysis.

Abstract: We report herein that the Ir and Cu(I) bis-metal catalyzed reductive alkynylation of amides, a method that we developed previously, can be extended to 6-, 7-, and 8-membered lactams. The catalytic reductive alkynylation of 6-methyl-2-piperidinones and its 3-benzyloxy derivative proceeded with 2.3: 1 to 7: 1 2,6-*trans*/cis diastereoselectivities. The resulting piperidines were converted into alkaloids (±)-solenopsin, (±)-solenopsin A, and (+)-julifloridine all in only one step. This two-step approach to the alkaloids is much shorter and much efficient than the conventional multistep methods.

2-Substituted, 2,6-disubstituted piperidines, and 2,6-disubstituted 3-piperidinols constitute an important class of alkaloids[1,2] (cf. **1**-**6** in Figure 1). The key structural features also found in many structurally complex polycyclic alkaloids[1b,2h] and medicinal agents such as (+)-L-733,060 (**7**), which is a potent and selective nonpeptide antagonists of neurokinin-1 (NK-1) substance P receptor. The broad spectrum of bioactivities exhibited by these alkaloids rend them attracted targets for many synthetic groups, and a number of synthetic strategies and methods have been developed.[1-3] Among them, the conversion based on the reductive alkylation of amides/ lactams (Scheme 1, a) turned out to be indispensable for many approaches.[1-3] However, due to the high stability of amides/ lactams, until recent years,[3] most approaches relied on multistep methods (Scheme 1, a).[2] With the contex of developing efficient synthetic methodologies,[4] in the last decade, much efforts have been devoted to develop mild methods for the direct reductive alkylation of amides/ lactams, which resulted in a number of useful synthetic protocols.[5,6] The latest progress is undoubtedly the catalytic reductive alkylation/ functionalization.[7] Despite the exciting progress, the total synthesis of alkaloids based on the catalytic reductive alkylation of amides remains rare.[8] Recently, our group has developed an Ir and Cu sequential catalysis for the direct reductive alkynylation of amides (Scheme 1, b).[7c]

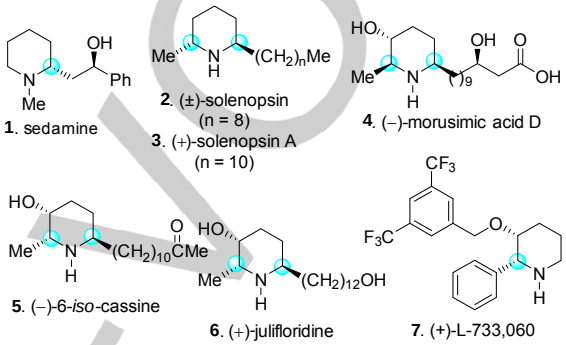
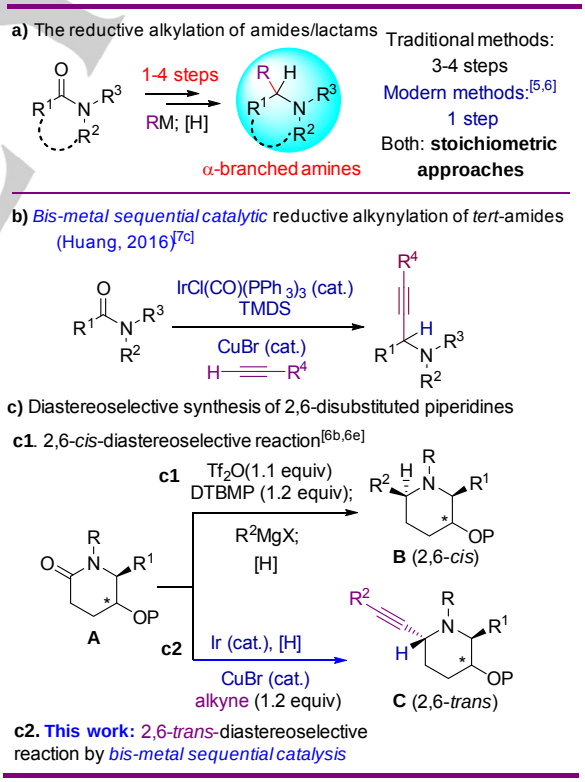


Figure 1. Representative 2-substituted, 2,6-disubstituted piperidine, and 2,6-dialkyl-3-piperidinol alkaloids.



Scheme 1. a. A key transformation in the synthesis of alkaloids and medicinal agents; b. Catalytic reductive alkynylation of *tert*-amides; c1. Reductive alkylation leading to *cis*-2,6-dialkylpiperidines; c2. This work.

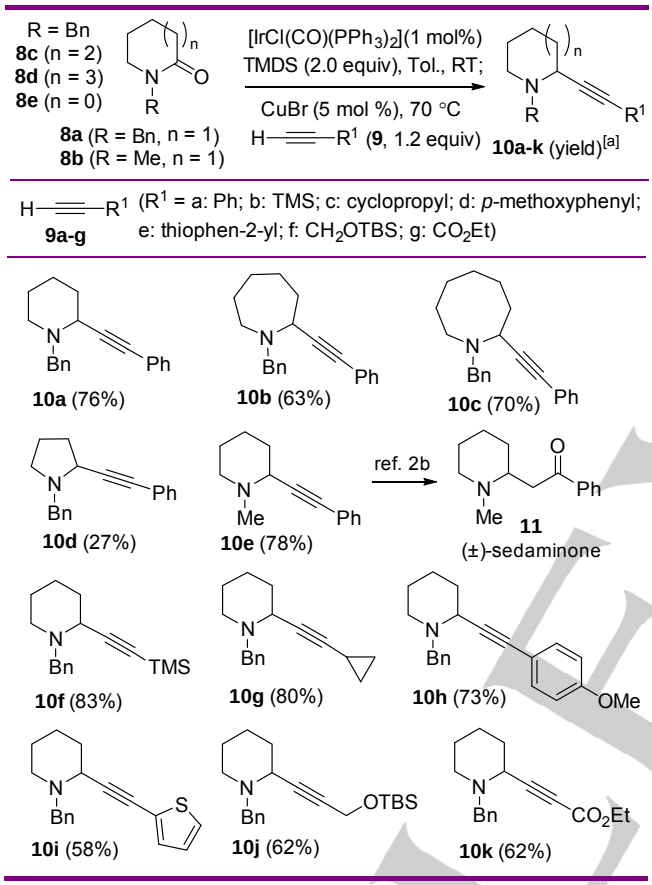
On the other hand, previously, we have disclosed the asymmetric synthesis of several piperidine alkaloids including (–

[a] *Department of Chemistry, Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China*
E-mail: pghuang@xmu.edu.cn; Homepage URL: http://huangpeiqiang.xmu.edu.cn/en/Home.htm
[b] *Current address:* International Collaborative Laboratory of 2D Materials for Optoelectronic Science & Technology of Ministry of Education, Engineering Technology Research Center for 2D Materials Information Functional Devices and Systems of Guangdong Province, Institute of Microscale Optoeletronics, Shenzhen University, Shen Zhen, 518060, China
[‡] Wei Ou and Guang-Sheng Lu contributed equally to this work.

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201901752.

10.1002/ejoc.201901752

)-cassine[6b] and (–)-morusimic acid D (**4**),[6e] two alkaloid possess a 2,6-*cis*-stereochemistry (Figure 1 and Scheme 1, c1). We envisaged that our bis-metal catalyzed reductive alkynylation method[7c] would provide an opportunity to establish a 2,6-*trans*-stereochemistry aound piperidine ring (Scheme 1, c2). We reported herein an extension of our method from tertiary amide to lactam substrates, which resulted in a direct, catalytic entrance to 2,6-*trans*-disubstituted piperidines (Scheme 1, c2), and the application of this methodology to the concise diastereoselective total synthesis of 2,6-*trans*-dialkylpiperidine alkaloids.



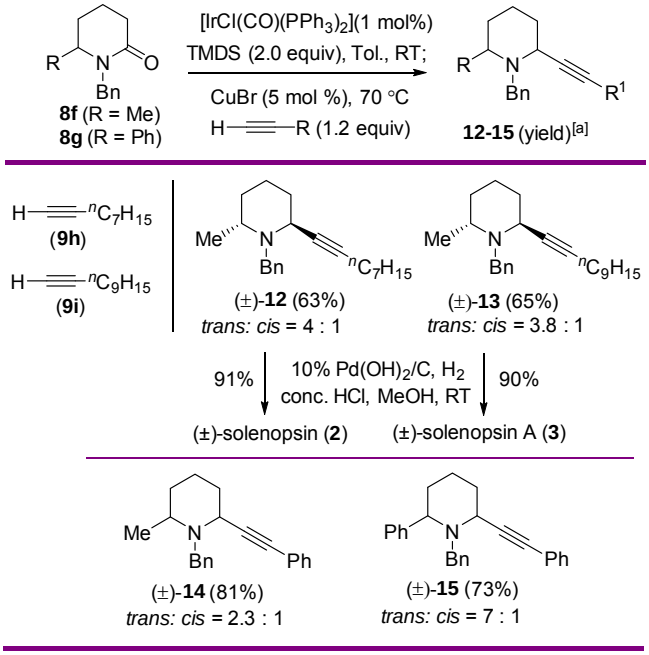
Scheme 2. Scope of the one-pot Ir- and Cu-catalyzed reductive alkynylation of lactams. [a] yield of isolated product.

At the outset of our investigation, the catalytic reductive phenylethynylation of commercially available *N*-benzyl δ-lactam (**8a**) was examined. According to our previously established method,[7c] a toluene solution of *N*-benzyl δ-lactam (**8a**) was treated with 1 mol% of Vaska's complex [IrCl(CO)(PPh_3)$_2$], 2.0 equiv. of TMDS,[9] 1.2 equiv. of phenylethyne (**9a**), and 5 mol% of CuBr at 70 °C. As expected, the cyclic propargylic amine **10a** was obtained in 76% yield (Scheme 2). Encouraged by this result, scope of the method was next examined and the results are summarized in Scheme 2. The reaction can be extended to seven membered and eight membered lactams **8c** and **8d**, which yielded **10b** and **10c** in 63% and 70% yields, respectively. To our surprise, the catalytic reductive alkynylation of *N*-benzyl γ-lactam (**8e**) gave the desired product **10d** in a low yield even after many trials (for the complete list summarizing the results, see: Table S1 in the supporting information). The reductive phenylethynation of *N*-methyl δ-lactam (**8b**) proceeded smoothly to afford **10e** in 78% yield. It is worth noting that compound **10e** has been synthesized by Takahata via a complex one-pot three-step protocol from thiolactam, and converted in one-pot to sedaminone (**11**).[2b] The latter was suggested to be a biosynthetic precursor of sedamine (**1**),[10a,b] an alkaloid belongs to the *Sedum* family. Interestingly, both enantiomers of sedamine (**1**) have been found in many other *Sedum* species.[10c] The reaction was next extended to other terminal alkyne nucleophiles **9b**-**9g**, and the corresponding propargylic piperidine derivatives **10f** – **10k** were obtained in 58% - 83% yields, reflecting the wide scope with respect to alkynes. Notably, the successful incorporation of functional groups such as silyloxylmethyl and ester groups affords the option for further transformations.

With the Ir and Cu-bis-catalytic alkynylation of lactam ensured, we then addressed the synthesis of 2,6-dialkylpiperidines which constitute a class of bioactive alkaloids isolated from both plant and animal kingdoms.[1a] Both 2,6-*cis* and 2,6-*trans*-dialkyl piperidines and 3-piperidinols exist among this class of natural products.[1] To get insight into the stereochemical outcome of the reductive alkynylation reaction, a racemic synthesis of the fire ant venom alkaloid solenopsin (**2**), isolated from *Solenopsis invitica*,[11] was envisaged. It is worth noting that some members of this family of alkaloids were found to display cytotoxic, insecticidal, hemolytic, antibacterial, antifungal and necrotic properties.[12] For example, solenopsin A (**3**) was reported to inhibit the regulator protein phosphatidylinositol-3-kinase (PI3K) which involves in controlling apoptosis, proliferation and angiogenesis.[12c] Such Insect toxins have been recognized as selective pharmacological tools and drug/chemical leads.[12d]

Our synthesis of solenopsin (**2**)[13] started from commercially available racemic *N*-benzyl-6-methylpiperidin-2-one (**8f**) (Scheme 3). Bis-catalytic reductive alkynylation of **8f** with non-1-yne (**9h**) at 70 °C yielded predominantly the *trans* propargylic piperidine **12** in 63% yield (dr = 4: 1). The stereochemistry of the major diastereomer was deduced from the alkaloid **2**, which was obtained by the *one-pot* catalytic hydrogenation - hydrogenolysis of the major diastereomer **12**. The spectral data of our synthetic product (**2**) match those reported for the natural product.[13] Similarly, bis-catalytic reductive alkynylation of **8f** with undec-1-yne (**9i**) yielded propargylic piperidine **13** and its diastereomer in a 3.8: 1 ratio in a combined yield of 77%. Subjecting **13** to the catalytic hydrogenation conditions proceeded with concomitant hydrogenation to produce (±)-solenopsin A (**3**) in 90% yield. The spectral data of **3** are identical with those reported in the literature.[1j,k,o]

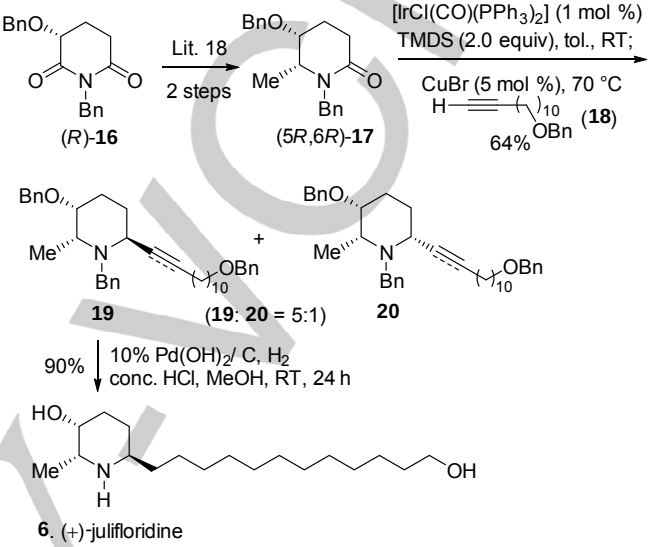
To probe the effect of substituent at C6 of lactam **8** on the diastereoselectivity of the reaction, the reductive phenylethynations of both 6-methyllactam **8f** and 6-phenyllactam **8g** were examined (Scheme 3). The former afforded **14** as a 2.3:1 (*trans/cis*) diastereomeric mixture in 81% yield, whereas the latter yielded **15** as a 7:1 (*trans/cis*) diastereomeric mixture in 81% yield, reflecting the dominant effect of steric hindrance at C6 on the diastereoselectivity.



Scheme 3. Ir- and Cu-catalyzed reductive alkynylation of 6-substituted piperidin-2-ones and the total synthesis of fire ant venom alkaloids solenopsin (**2**) and solenopsin A (**3**). [a] yield of isolated product.

Next, we turned our attention to the enantioselective synthesis of (+)-julifloridine (**6**), an alkaloid isolated from *Prosopis juliflora* DC (mesquite).[14] This natural poisoning alkaloid and extracts from *Prosopis juliflora* have been reported to exhibit neurotoxicity,[15a] *in vivo* antimalarial,[15b] and antimicrobial activities.[15c] It is worth mentioning that the 2-methyl-3-hydroxypiperidine ring system with the same stereochemical pattern is also found in other piperidine alkaloids,[16a] and some have been reported to show DNA-domaging activity.[16b] However, among this sub-class of alkaloids,[1c,e,f] less efforts have been devoted to the synthesis of julifloridine (**6**), only two enantioselective syntheses,[17a,b] an enantioselective synthesis of its antipode,[17c] and a racemic synthesis[17d] have been reported.

Our synthesis started from (*R*)-*N*-benzyl-3-benzyloxy glutarimide (**16**)(Scheme 4), a versatile chiral building block developed by our group.[1g] Following a protocol that we developed previously, methyl Grignard addition followed by boron trifluoride etherate-mediated reduction with zinc borohydride[18] produced chemo- and diastereo-selectively (5*R*,6*R*)-5-benzyloxy-2-piperidinone **17**[2d] and its diastereomer (no shown) in about 60% yield over two steps. Subjection of the major diastereomer (5*R*,6*R*)-**17** to the catalytic reductive alkynylation with alkyne **20** yielded two diastereomers **19** and **20** in 64% yield with a diastereomeric ratio of 5:1, from which a sample of propargylic amine **19** containing a small amount of the corresponding partially reduced alkene was isolated. The stereochemistry of the major diastereomer **19** was deduced from the final product. Subjection of the sample **19** to Pearlman's catalyst-catalyzed hydrogenation/ hydrogenolysis under acidic conditions led directly to the formation of (+)-julifloridine (**6**) as a white solid {Mp 83-85 °C, lit.[17a] 85-87.5 °C, lit.[17b] 82-83 °C; lit.[21c] 81-83.5 °C; $[\alpha]_D^{20}$ = +13.3 (*c* 0.55, MeOH), lit.[17a] $[\alpha]_D^{25}$ = +18 (*c* 0.84, MeOH), lit.[17b] $[\alpha]_D^{20}$ = +7.3 (*c* 0.23, MeOH), lit.[17c] $[\alpha]_D^{20}$ = –8.2 (*c* 0.34, MeOH) for the antipode}. It is worth noting that during this transformation, hydrogenation of the triple bond, double bond, and *N,O,O*-tris-debenzylation reactions occurred in one-pot at RT for 24 h to afford the alkaloid **6** in high yield (90%).



Scheme 4. Concise enantioselective total synthesis of (+)-julifloridine.

In summary, we have demonstrated that the direct reductive alkynylation of amides based on the Ir and Cu(I) bis-metal sequential catalysis can be extended to 6-, 7-, and 8-membered lactams. The catalytic reductive alkynylations of *N*-benzyl-6-methylpiperidin-2-one and its 3-benzyloxy derivative resulted in the selective formation of 2,6-*trans*-disubstituted piperidines that is complementary to the typically 2,6-*cis*-diastereoselective methods.[6b,6e] The efficiency of this methodology was highlighted by the procedure-economical total syntheses of three alkaloids, (±)-solenopsin (**2**), (±)-solenopsin A (**3**), and (+)-julifloridine (**6**) with 2,6-*trans:cis* diastereoselectivities ranged from 3.8: 1 to 5: 1. As a comparison, the synthesis of structurally similar (–)-6-*iso*-cassine (**5**) from (–)-**17** required 10 steps.[2d]

Experimental Section

General procedure for the bis-catalytic reductive alkynylation of lactams

In a glove box charged with an atmosphere of nitrogen, $IrCl(CO)(PPh_3)_2$ (8 mg, 0.01 mmol, 1 mol %) was added to a dried 10-mL round-bottom flask equipped with a magnetic stirring-bar. The flask was then removed from the glove box. A solution of a lactam (1.0 mmol, 1.0 equiv) in toluene (5 mL), 1,1,3,3-tetramethyldisiloxane (0.36 mL, 2.0 mmol, 2.0 equiv) were successively added to the flask at room temperature. After being stirred for 30 min, the resulting mixture and a terminal alkyne (1.2 mmol, 1.2 equiv) were sequentially added to a suspension of CuBr (7 mg, 0.05 mmol, 5 mol %) in toluene (3 mL) in a 25-mL round-bottom flask under argon. The mixture was stirred at 70 °C for 8 h. Then, the mixture was concentrated under reduced pressure, and the residue was purified

by flash column chromatography (FC) on silica gel to afford the corresponding propargylic amine.

General procedure for the one-pot catalytic hydrogenation and hydrogenolysis of *N*-benzyl-α-alkynylpiperidines

A stirred mixture of a *N*-benzyl-α-alkynylpiperidine (1.0 mmol), 0.5 mL conc. HCl, and 10% $Pd(OH)_2/C$ (10% wt) in methanol (5 mL) was hydrogenated under 1 atm of hydrogen (balloon) at room temperature. When the reaction was judged to be completed by TLC monitoring, the mixture was filtered under a reduced pressure, and the residue was washed with methanol (5 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography (FC) on silica gel to afford the corresponding product.

Acknowledgements

The authors are grateful for the financial support provided by the National Key R&D Program (2017YFA0207302) and the National Natural Science Foundation of China (21931010 and 21672176).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Catalysis • Reductive alkynylation • Lactams • Alkaloids • Stereoselective synthesis

[1] a) M. Schneider, *Alkaloids: Chemical and Biological Perspectives*, Vol. 10, ed. by S. W. Pelletier, Pergamon: Oxford, 1996, 55–299; b) A. K. Mailyan, J. A. Eickhoff, A. S. Minakova, Z. H. Gu, P. Lu, A. Zakarian, *Chem. Rev.* **2016**, *116*, 4441–4557; c) C. Ande, S. Dubbu, A. K. Verma, Y. D. Vankar, *Tetrahedron Lett.* **2018**, *59*, 1879-1895; d) N. Kandepedu, I. Abrunhosa-Thomas, Y. Troin, *Org. Chem. Front.* **2017**, *4*, 1655-1704; e) M. A. Wijdeven, J. Willemsen, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2010**, 2831-2844; f) S. D. Koulocheri, E. N. Pitsinos, S. A. Haroutounian, *Curr. Org. Chem.* **2008**, *12*, 1454-1467; g) P.-Q. Huang, *Synlett* **2006**, 1133-1147; h) N. Toyooka, H. Nemoto, "Synthetic Studies on Biologically Active Alkaloids Starting from Lactam-Type Chiral Building Blocks", in *Studies in Natural Products Chemistry*, Vol. 29, Atta-ur-Rahman (Ed.), Elsevier B.V. 2003. i) S. Leclercq, D. Daloze, J.-C. Braekman, *Org. Prep. Proced. Int.* **1996**, *28*, 499-543. For selected examples, see: j) D. S. Grierson, J. Royer, L. Guerrier, H.-P. Husson, *J. Org. Chem.* **1986**, *51*, 4475–4477; k) N. Girard, J.-P. Hurvois, L. Toupet, C. Moinet, *Synth. Commun.* **2005**, *35*, 711–723; l) X. Wang, Y. Dong, J. Sun, X. Xu, R. Li, Y. Hu *J. Org. Chem.* **2005**, *70*, 1897-1900; m) S. D. Bergman, T. E. Storr, H. Prokopcová, K. Aelvoet, G. Diels, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10393-10398; n) S. Grélaud, J. Lusseau, S. Massip, Y. Landais, *Adv. Synth. Catal.* **2017**, *359*, 2434-2441; o) W. Chen, L. Ma, A. Paul, D. Seidel, *Nat. Chem.* **2018**, *10*, 165-169.

[2] For selected examples, see: a) K. Shiosaki, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 1229–1239; b) K. Takahashi, E.-C. Wang, T. Yamazaki, H. Takahata, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1211 –1214; c) W. J. Klaver, H. Hiemstra, N. Speckamp, *J. Am. Chem. Soc.* **1989**, *111*, 2588–2595; d) N. Toyooka, Y. Yoshida, Y. Yotsui, T. Momose, *J. Org. Chem.* **1999**, *64*, 4914–4919; e) P. Schär, P. Renaud, *Org. Lett.* **2006**, *8*, 1569–1571; f) T. Murai, R. Toshio, Y. Mutoh, *Tetrahedron* **2006**, *62*, 6312−6320; g) T. Mitamura, A. Ogawa, *Org. Lett.* **2009**, *11*, 2045–2048; h) A. S. Lee, B. B. Liau, M. D. Shair, *J. Am. Chem. Soc.* **2014**, *136*, 13442-13452.

[3] For a one-pot reductive alkynylation using alkynyl boranes, see: a) M. Yamaguchi, I. Hirao, *Tetrahedron Lett.* **1983**, *24*, 1719–1722; for a one-pot reductive arylation, see: b) Y. C. Hwang, M. Chu, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 3885–3890, *correction*: ibid, **1986**, *51*, 2156.

[4] a) P.-Q. Huang, Z.-J. Yao, P. H. Richard, Eds. *Efficiency in Natural Product Total Synthesis*. John Wiley & Sons, Inc.: Hoboken, USA, 2018; for selected examples, see: b) H. Geng, P.-Q. Huang, *Chin. J. Chem.* **2019**, *37*, 811-816; c) S.-R. Wang, P.-Q. Huang, *Chin. J. Chem.* **2019**, *37*, 887-891.

[5] For reviews, see: a) D. Seebach, *Angew. Chem., Int. Ed.* **2011**, *50*, 96-101; b) V. Pace, W. Holzer, *Aust. J. Chem.* **2013**, *66*, 507–510; c) T. Sato, N. Chida, *Org. Biomol. Chem.* **2014**, *12*, 3147–3150; d) V. Pace, W. Holzer, B. Olofsson, *Adv. Synth. Catal.* **2014**, *356*, 3697–3736; e) T. Sato, N. J. Chida, *Synth. Org. Chem., Jpn.* **2016**, *74*, 599–610; f) D. Kaiser, N. Maulide, *J. Org. Chem.* **2016**, *81*, 4421-4428; g) P.-Q. Huang, *Acta Chim. Sinica* **2018**, *76*, 357 –365; h) D. Kaiser, A. Bauer, M. Lemmerer, N. Maulide, *Chem. Soc. Rev.* **2018**, *47*, 7899–7925; i) T. Sato, M. Yoritate, H. Tajima, N. Chida, *Org. Biomol. Chem.* **2018**, *16*, 3864-3875.

[6] For representative examples, see: a) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2010**, *49*, 3037−3040; b) K.-J. Xiao, Y. Wang, K.-Y. Ye, P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 12792–12796; c) Y. Oda, T. Sato, N. Chida, *Org. Lett.* **2012**, *14*, 950–953; d) K.-J. Xiao, A. E Wang, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 8314−8317; e) K.-J. Xiao, Y. Wang, Y.-H. Huang, X.-G. Wang, J.-C. Liao, P.-Q. Huang, *J. Org. Chem*. **2013**, *78*, 8305-8311; f) P.-Q. Huang, Y.-H. Huang, K.-J. Xiao, Y. Wang, X.-E. Xia, *J. Org. Chem.* **2015**, *80*, 2861−2868; g) S. Itabashi, M. Shimomura, M. Sato, H. Azuma, K. Okano, J. Sakata, H. Tokuyama, *Synlett* **2018**, *29*, 1786-1790; h) Y.-H Huang, S.-R. Wang, D.-P. Wu, P.-Q. Huang, *Org. Lett.* **2019**, *21*, 1681-1685; for reductive functionalization of *N*-methoxyamides, see: i) K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Angew. Chem. Int. Ed.* **2010**, *49*, 6369–6372; j) G. Vincent, R. Guillot, C. Kouklovsky, *Angew. Chem. Int. Ed.* **2011**, *50*, 1350–1353; k) Y. Yanagita, H. Nakamura, K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Chem. Eur. J.* **2013**, *19*, 678–684; l) M. Yoritate, T. Meguro, N. Matsuo, K. Shirokane, T. Sato, N. Chida, *Chem. Eur. J.* **2014**, *20*, 8210-8216; m) M. Nakajima, Y. Oda, T. Wada, R. Minamikawa, K. Shirokane, T. Sato, N. Chida, *Chem. Eur. J.* **2014**, *20*, 17565-17571.

[7] a) A. W. Gregory, A. Chambers, A. Hawkins, P. Jakubec, D. J. Dixon, *Chem. Eur. J.* **2015**, *21*, 111−114; b) M. Nakajima, T. Sato, N. Chida, *Org. Lett.* **2015**, *17*, 1696−1699; c) P.-Q. Huang, W. Ou, F. Han, *Chem. Commun.* **2016**, *52*, 11967−11970; d) L.-G. Xie, D. J. Dixon, *Chem. Sci.* **2017**, *8*, 7492−7497; e) T. O. Ronson, E. Renders, B. F. Van Steijvoort, X. B. Wang, C. C. D. Wybon, H. Prokopcová, L. Meerpoel, B. U. W. Maes, *Angew. Chem. Int. Ed*. **2019**, *58,* 482-487; f) Y. Takahashi, T. Sato, N. Chida, *Chem. Lett.* **2019**, *48*, 1138-1141; see also: g) S. Katahara, S. Kobayashi, K. Fujita, T. Matsumoto, T. Sato, N. Chida, *J. Am. Chem. Soc.* **2016**, *138*, 5246−5249; h) S. Katahara, S. Kobayashi, K. Fujita, T. Matsumoto, T. Sato, N. Chida, *Bull. Chem. Soc. Jpn.* **2017**, *90*, 893–904; i) X.-N. Hu, T.-L. Shen, D.-C. Cai, J.-F. Zheng, P.-Q. Huang, *Org. Chem. Front.* **2018**, *5*, 2051−2056; j) L.-G. Xie, D. J. Dixon, *Nat. Commun.* **2018**, *9*, 2841; for Ir-catalyzed reductive functionalization of secondary amides, see: k) W. Ou, F. Han, X.-N. Hu, H. Chen, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2018**, *57*, 11354-11358; l) Y. Takahashi, R. Yoshii, T. Sato, N. Chida, *Org. Lett.* **2018**, *20*, 5705–5708.

[8] For applications in the total synthesis, see: a) P. W. Tan, J. Seayad, D. J. Dixon, *Angew. Chem. Int. Ed.* **2016**, *55*, 13436–13440; b) M. Yoritate, Y. Takahashi, H. Tajima, C. Ogihara, T. Yokoyama, Y. Soda, T. Oishi, T. Sato, N. Chida, *J. Am. Chem. Soc.* **2017**, *139*, 18386–18391; c) T. Sugai, Y. Okuyama, J. Shin, S. Usui, S. Hisada, R. Osanai, T. Oishi, T. Sato, N. Chida, *Chem. Lett.* **2018**, *47*, 454–457; d) S. Yamamoto, Y. Komiya, A. Kobayashi, R. Minamikawa, T. Oishi, T. Sato, N. Chida, *Org. Lett.* **2019**, *21*, 1868–1871.

[9] a) Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto, H. Nagashima, *Chem. Commun*. **2009**, 1574−1576; b) A. Tahara, I. Kitahara, D. Sakata, Y.

Kuninobu, H. Nagashima *J. Org. Chem*. **2019**, *84*, DOI: 10.1021/acs.joc.9b02267.

[10] a) H. C. Beyerman, P. H. Enthoven, *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 82-84; b) H. C. Beyerman, W. Eveeleens, Y. M. F. Muller, *Recl. Trav. Chem. Pays-Bas* **1956**, *75*, 63-74.

[11] a) T. H. Jones, M. S. Blum, H. M. Fales, *Tetrahedron* **1982**, *38*, 1949-1158; b) S. Leclerq, I. Thirionet, F. Broeders, D. Daloze, R. Van der Meer, J. C. Braeckman, *Tetrahedron* **1994**, *50*, 8465-8478.

[12] a) M. S. Blum, J. R. Walker, P. S. Callahan, A. F. Novak, *Science* **1958**, *128*, 306-307; b) G. B. Yi, D. McClendon, D. Desaiah, J. Goddard, A. Lister, J. Moffitt, R. K. Vander Meer, R. deShazo, K. S. Lee, R. W. Rockhold, *Int. J. Toxicol.* **2003**, *22*, 81-86; c) I. Karlsson, X. Zhou, R. Thomas, A. T. Smit, M. Y. Bonner, P. Bakshi, A. K. Banga, J. P. Bowen, G. Qabaja, S. L. Ford, M. D. Ballard, K. S. Petersen, X. Li, G. Chen, B. Ogretmen, J. Zhang, E. B. Watkins, R. S. Arnold, J. L. Arbiser, *Vasc. Cell* **2015** 7: 5; d) H. S. Kachel, S. D. Buckingham, D. B. Sattelle, *Curr. Opin. Insect Sci.* **2018**, *30*, 93-98.

[13] To our surprise, only one total (enantioselctive) syntheis of solenopsin has been reported: M. Medjahdi, J. C. González-Gómez, F. Foubelo, M. Yus, *Heterocycles* **2012**, *86*, 727-734.

[14] a) V. U. Ahmad, A. Basha, W. *Z.* Haque, *Naturforsch. B: Anorg. Chem. Org. Chem.* **1978**, *33B,* 347-348; b) V. U. Ahmad, S. *Z.* Qazi, *Naturforsch. B: Anorg. Chem. Org. Chem.* **1983**, *38B,* 660-660.

[15] a) V. D. A. da Silva, A. M. M. da Silva, J. H. Castro e Silva, S. L. Costa, *Neurotoxicity Res.* **2018**, *34*, 878–888; b) R. Batista, C. C. Santana, A. V. Azevedo-Santos, A. M. Suarez-Fontes, J. L. de Almeida Antunes Ferraz, L. A. M. Silva, M. A. Vannier-Santos, *J. Funct. Foods* **2018**, *44*, 74-78; c) A. Aqeel, A. K. Khursheed, A. Viqaruddin, Q. Sabiha, *Arzneimittel-Forschung/Drug Res.* **1989**, *39-1*, 652-655.

[16] a) V. S. Bolzani, A. A. L. Gunatilaka, D. G. I. Kingston, *Tetrahedron* **1995**, *51*, 5929-5934; b) C. Viegas, V. S. Bolzani, M. Furlan, E. J. Barreiro, M. C. M. Young, D. Tomazela, M. N. Eberlin, *J. Nat. Prod.* **2004**, *67*, 908–910.

[17] a) T. Kiguchi, M. Shirakawa, R. Honda, I. Ninomiya, T. Naito, *Tetrahedron* **1998**, *54*, 15589-15606; b) A. Lemire, A. B. Charette, *Org. Lett.* **2005**, *7*, 2747-2750; c) H. Zhai, M. Parvez, T. G. Back, *J. Org. Chem.* **2007**, *72*, 3853–3858; d) M. Paterne, E. Brown, *C. R. Acad. Sci. Paris Ser. 2* **1983**, *296*, 433-434.

[18] L.-X. Liu, K.-J. Xiao, P.-Q. Huang, *Tetrahedron* **2009**, *65*, 3834–3841.

10.1002/ejoc.201901752

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

*Wei Ou, Guang-Sheng Lu, Dong An, Feng Han, and Pei-Qiang Huang**

Page No. – Page No.
Two-step Catalytic Transformation of *N*-Benzyllactams to alkaloids (±)-Solenopsin, (±)-Solenopsin A, and (+)-Julifloridine

A procedure-economical synthesis of 2,6-*trans*-substituted piperidine alkaloids is described. The method consists of Ir and Cu catalyzed reductive alkynylation of *N*-benzyllactams and tandem catalytic hydrogenation-hydrogenolysis.

- Direct transformation of lactams