Natural Product Synthesis

DOI: 10.1002/anie.201306369

Divergent and Efficient Syntheses of the *Lycopodium* Alkaloids (−)-Lycojaponicumin C, (−)-8-Deoxyserratinine, (+)-Fawcettimine, and (+)-Fawcettidine**

Si-Hua Hou, Yong-Qiang Tu, Lin Liu, Fu-Min Zhang, Shao-Hua Wang,* and Xiao-Ming Zhang*

The fawcettimine class of *Lycopodium* alkaloids are a class of structurally unique natural molecules with more than 80 members,[1] among which lycojaponicumin C (**1**),[2] 8-deoxyserratinine (**2**),[3] fawcettimine (**3**),[4] and fawcettidine (**4**)[5] are representative ones (Figure 1). In particular, the alkaloid **1** isolated by Yu and co-workers from the traditional Chinese medicine (*L. japonicum* THUNB) possesses biological activity.[2] The structures of the alkaloids of the fawcettimine class feature the fused tetracyclic ABCD frameworks including two common AB rings and two differently-sized CD rings together with highly crowded quaternary stereocenters. Because of their wide-ranging biological activities and challenging structures, syntheses of these alkaloids have attracted great attention, and several total syntheses have been accomplished.[6,7] Many of these strategies make use of the key 6/5/9 tricyclic intermediate **7** (Scheme 1), which is prepared at least in 10 steps from readily available material.[6f,i] Using a similar intermediate, we also have finished the total synthesis of sieboldine A.[7f] Our next attempt toward this subject is to explore a more efficient divergent strategy through designing a versatile common intermediate such as **8**, which contains a 6/5/5 polycyclic system rather than the 6/5/9 system in **7** but contains an azido chain. We expect such an advanced intermediate allows access not only to the alkaloids **2**–**4** via subintermediate **6**, but also to other important molecules. Here, we report the first asymmetric total synthesis of **1** and the improved total syntheses of **2**–**4** by using this proposal.

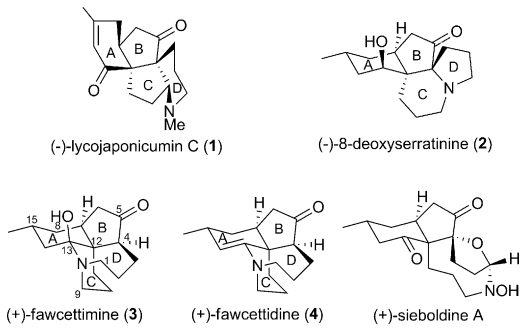
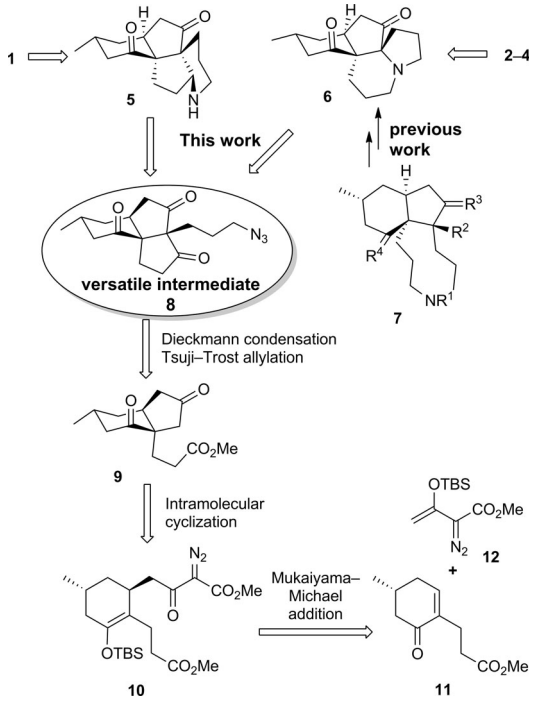


Figure 1. Representative alkaloids of the fawcettimine class.



Scheme 1. Retrosynthetic analysis of **1**–**4**. TBS = *tert*-butyldimethylsilyl.

Our retrosynthetic analysis was illustrated in Scheme 1. Based on the reported biogenetic pathway,[2] the target molecules **1** and **2**–**4** could be derived from **5** and **6**, respectively. According to our hypothesis above, both **5** and **6** would be expected to be assembled from the key advanced

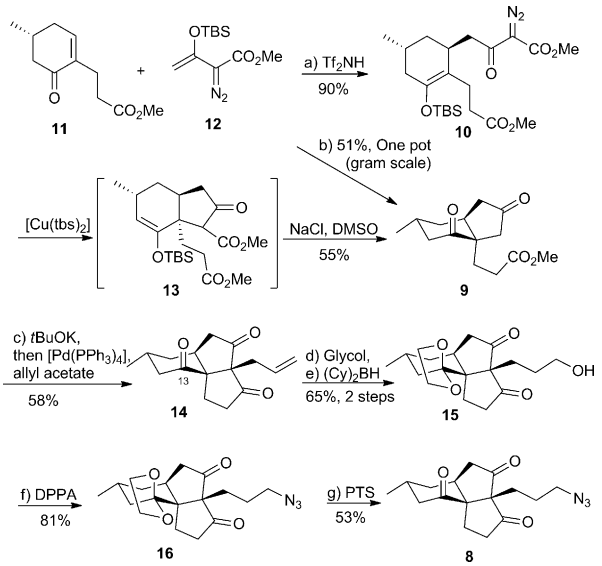
[*] S.-H. Hou, Prof. Dr. Y.-Q. Tu, L. Liu, Prof. Dr. F.-M. Zhang, Prof. Dr. S.-H. Wang, Dr. X.-M. Zhang
State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University
Lanzhou 730000 (P. R. China)
E-mail: tuyq@lzu.edu.cn
Prof. Dr. S.-H. Wang
School of Pharmacy, Lanzhou University
Lanzhou 730000 (P. R. China)
E-mail: wangshh@lzu.edu.cn

[**] This work was supported by the NSFC (21072085, 21102061, 21202073, 21290180, and 21272097), the "973" Program of MOST (2010CB833203), the "111" Program of MOE, and the Major Project of MOST (2012ZX 09201101-003). We thank Prof. Shi-Shan Yu of the Institute of Materia Medica Chinese Academy of Medical Sciences and Peking Union Medical College for providing a sample of **1**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306369.

6/5/5 tricyclic intermediate **8** through intramolecular aza-Wittig reaction and Schmidt N insertion, respectively. Furthermore, **8** would be generated from *cis*-6/5 bicyclic dione **9** through the sequent Dieckmann condensation/Tsuji–Trost allylation, then hydroboration and azidation. The dione **9** could be prepared from diazoenolate **10** by using our newly developed intramolecular carbene addition/cyclization.[8] The intermediate **10** could be prepared through Mukaiyama–Michael addition from known enone **11** and vinyl diazoacetate **12**.

Our synthesis commenced initially with the stepwise preparation of the *cis*-bicyclic dione **9** from **11**[9] and **12**[10] (Scheme 2). Although Doyle and co-workers reported an efficient Mukaiyama–Michael reaction with zinc triflate as

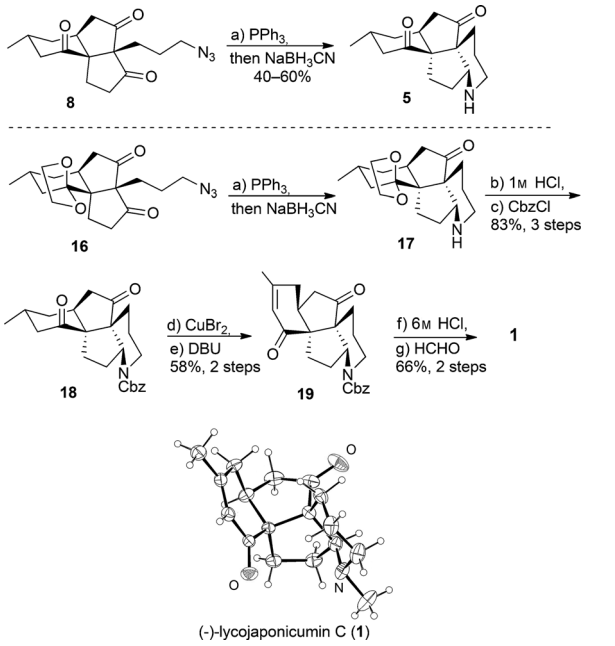


Scheme 2. Synthesis of the key intermediate **8**. Reagents and conditions: a) 1. Tf_2NH, CH_2Cl_2, −78 °C (90%), 2. $[Cu(tbs)_2]$, PhCl, 130 °C, then DMSO, NaCl, H_2O, 180 °C (55%); b) Tf_2NH, CH_2Cl_2, −78 °C, then $[Cu(tbs)_2]$, PhCl, 130 °C, then DMSO, NaCl, H_2O, 180 °C (51%, one pot); c) *t*BuOK, THF, reflux, then $[Pd(PPh_3)_4]$, allyl acetate, THF, 0 °C→60 °C (58%); d) PTS, glycol, benzene, reflux (76%); e) $BH_3{\cdot}Me_2S$, cyclohexene, THF, 0 °C, then $NaBO_3{\cdot}4H_2O$, H_2O, RT (85%); f) DPPA, DIAD, PPh_3, THF, 0 °C→ RT (81%); g) PTS, acetone/H_2O (10:1), reflux (53%). Tf_2NH = triflimide, $[Cu(tbs)_2]$ = bis(*N-tert*-butylsalicylaldiminato) copper(II), DMSO = dimethylsulfoxide, *t*BuOK = potassium *tert*-butoxide, $[Pd(PPh_3)_4]$ = tetrakis(triphenylphosphine) palladium(0), PTS = *p*-toluenesulfonic acid, Glycol = ethylene glycol, $(Cy)_2BH$ = bis(cyclohexanyl)borane, RT = room temperature, DPPA = diphenylphosphoryl azide, DIAD = diisopropyl azodicarboxylate.

catalyst for the construction of functionalized diazoacetoacetates,[11] unfortunately such a condition was not applicable to our system. Replacement of the catalyst with triflimide could realize the expected reaction to give the desired product **10** in 90% yield as a single diastereomer. Then we turned our focus on the designed intramolecular carbene addition/cyclization[12] for constructing the dione **9**. After the screening of various catalysts, $[Cu(tbs)_2]$ gave a satisfying result. Notably in this experimental process, a slow addition of **10** to a solution of $[Cu(tbs)_2]$ (20 mol%) in PhCl at 130 °C was crucial for forming the intermediate **13**,[13] which was directly subjected to decarboxylation at 180 °C without purification to provide **9**. In our later experiment, the dione **9** was prepared in a one-pot manner and on gram scale directly from **11** and **12** with a total yield of 51%. Next, treatment of ketone ester **9** with *t*BuOK in THF at reflux gave an enolate of tricyclic trione, which was then quenched with allyl acetate[14] to deliver the olefin **14** in 58% yield. At this stage, we successfully assembled the tricyclic framework **14** with all carbon atoms of the key intermediate **8** only by two consecutive one-pot procedures in 30% total yield. Subsequently, we expected direct hydroboration and azidation of **14** would lead to the intermediate **8**. However, hydroboration of the olefin **14** did not afford the desired primary alcohol, which might be attributed to the fact that the C13 carbonyl group was unprotected. Thus protection of C13 carbonyl with glycol and then hydroboration of the double bond under conditions reported by Kabalka and co-workers[15] furnished the primary alcohol **15** in 65% yield over two steps. Mitsunobu reaction[16] of the alcohol with diphenylphosphoryl azide (DPPA) produced azidoketone **16**, the structure of which was confirmed by X-ray crystallographic analysis.[17] Final removal of the glycol afforded the key intermediate **8** in 53% yield.

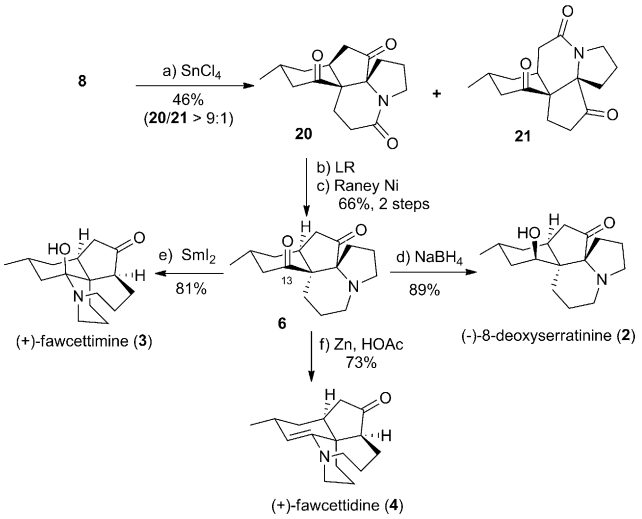
Having the key advanced intermediate **8** in hand, we then attempted the regioselective aza-Wittig reaction[18] to construct the last ring D for completing the total synthesis of alkaloid **1**. Initially, the use of unprotected **8** afforded the compound **5** and other inseparable materials in moderate yield. Treatment of the protected azidodione **16** with PPh_3 in toluene followed with $NaBH_3CN$ in HOAc gave tetracyclic amine **17** as a single product in excellent yield (Scheme 3).[19] Removal of the glycol of **17** with 1M HCl aqueous solution and protection of the secondary amine with CbzCl produced dione **18** in 83% overall yield from **16**. After extensive investigations of the olefination conditions,[20,21] bromination of **18** with $CuBr_2$[22] followed by dehydrobromination with DBU[23] afforded the enone **19** in 58% yield. Finally, the target alkaloid **1** was obtained by exchanging the Cbz group of **19** with a methyl group. Its structure was identical to the natural product sample as determined by spectroscopy and confirmed by X-ray crystallographic analysis.[17] As a result we successfully completed the first efficient asymmetric total synthesis of (−)-lycojaponicumin C (**1**) in 12 steps and 4.7% overall yield.

We then turned to investigate the intramolecular regioselective Schmidt N insertion to construct the 6/5 rings of the common intermediate **6** for the total syntheses of alkaloids **2**–**4**. Although the intramolecular Schmidt reaction has been proved as an efficient method for constructing the cyclic lactam and applied in syntheses of many alkaloids,[24] here the regioselective N insertion of a chained azide to one of the six possible positions of the trione **8** is challenging. Fortunately, by careful examination of the reaction conditions using various Lewis acids ($TiCl_4$, $BF_3{\cdot}Et_2O$, $SnCl_4$), protonic acids (TFA, TfOH, $ClSO_3H$), and solvents at different temperatures, the desired lactam **20** could be obtained in moderate yield under reaction with an excess of $SnCl_4$ (10 equiv) in refluxing toluene along with only one minor byproduct **21** (**20**/



Scheme 3. Synthesis of alkaloid **1**. Reagents and conditions: a) PPh_3, toluene, reflux, then MeOH, HOAc, $NaBH_3CN$, 0 °C; b) THF, 1 M HCl/H_2O, reflux; c) Na_2CO_3, CbzCl, THF/H_2O (1:1), RT (83 %, over 3 steps); d) $CuBr_2$, THF, RT; e) DBU, toluene, RT (58 %, over 2 steps); f) 6 M HCl/H_2O, reflux; g) HCHO/H_2O, $NaBH_3CN$, MeOH, 0 °C (66 %, over 2 steps). HOAc = acetic acid, CbzCl = benzyl chloroformate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

21 > 9:1; Scheme 4).[17,25] Subsequent treatment of lactam **20** with Lawesson's reagent in toluene followed by reduction of the resulting thiolactam[17] using Raney Ni[26] in EtOH gave the intermediate **6** in 66 % yield over two steps. Its spectroscopic data were identical to those reported.[6f,i,27] Thus, a very short synthesis of the key and common intermediate **6** was completed in 9 steps and 2 % overall yield.



Scheme 4. Syntheses of **2**–**4**. Reagents and conditions: a) $SnCl_4$, toluene, reflux (46 %, **20**/**21** > 9:1); b) LR, toluene, reflux; c) Raney Ni, EtOH, RT (66 %, over 2 steps); d) $NaBH_4$, MeOH, 0 °C (89 %); e) SmI_2, THF, H_2O, 0 °C (81 %); f) Zn, HOAc, reflux (73 %). LR = Lawesson's reagent.

Finally, the concise total syntheses of the other three alkaloids **2**–**4** were also finished according to the literature procedures.[6f,i] Selective reduction of the carbonyl at C13 of **6** with $NaBH_4$ gave (−)-8-deoxyserratinine (**2**) in 89 % yield. Selective cleavage of the C4–N bond of **6** with SmI_2 followed by a in situ aza-ketalization afforded (+)-fawcettimine (**3**) in 81 % yield.[28] Subjecting **6** to harsh reducing conditions (Zn/HOAc, 140 °C) effected the sequent C4–N cleavage, aza-ketalization, and dehydration to provide (+)-fawcettidine (**4**) in 73 % yield. The spectroscopic data for synthetic **2**–**4** were identical to those reported.[25]

In summary, we have explored a novel and divergent strategy[29] for syntheses of multiple alkaloids of the fawcettimine class and completed the first efficient asymmetric total synthesis of (−)-lycojaponicumin C (**1**) in 12 steps from the chiral enone **11** and the more concise improved total syntheses of the other three members **2**–**4** in 10 steps. A major innovation of this strategy involved the design of a versatile common tricyclic azidotrione intermediate **8**, which can undergo a series of transformations to reach the synthesis of not only above molecules **1**–**4** but possibly some other related members.

Received: July 22, 2013
Published online: ■■ ■■, ■■■■

Keywords: alkaloids · aza-Wittig reaction · divergent synthesis · natural products · Schmidt reaction

[1] For recent reviews of the *Lycopodium* alkaloids, see: a) W. A. Ayer, L. S. Trifonov in *The Alkaloids*, *Vol. 45* (Eds.: G. A. Cordell, A. Brossi), Academic Press, New York, **1994**, pp. 233–266; b) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752–772; c) J. Kobayashi, H. Morita in *The Alkaloids*, *Vol. 61* (Ed.: G. A. Cordell), Academic Press, New York, **2005**, pp. 1–57; d) Y. Hirasawa, J. Kobayashi, H. Morita, *Heterocycles* **2009**, *77*, 679–729; e) P. Siengalewicz, J. Mulzer, U. Rinner in *The Alkaloids*, *Vol. 72* (Eds.: H.-J. Knölker), Academic Press, New York, **2013**, pp. 1–151.

[2] X.-J. Wang, G.-J. Zhang, P.-Y. Zhuang, Y. Zhang, S.-S. Yu, X.-Q. Bao, D. Zhang, Y.-H. Yuan, N.-H. Chen, S.-G. Ma, J. Qu, Y. Li, *Org. Lett.* **2012**, *14*, 2614–2617.

[3] Y. Inubushi, H. Ishii, B. Yasui, T. Harayama, M. Hosokawa, R. Nishino, Y. Nakahara, *Yakugaku Zasshi* **1967**, *87*, 1394–1403.

[4] R. H. Burnell, *J. Chem. Soc.* **1959**, 3091–3093.

[5] R. H. Burnell, C. G. Chin, B. S. Mootoo, D. R. Taylor, *Can. J. Chem.* **1963**, *41*, 3091–3094.

[6] For reports on the total synthesis of 8-deoxyserratinine (**2**), fawcettimine (**3**), and fawcettidine (**4**), see: a) T. Harayama, M. Takatani, Y. Inubushi, *Chem. Pharm. Bull.* **1980**, *28*, 2394–2402; b) C. H. Heathcock, K. M. Smith, T. A. Blumenkopf, *J. Am. Chem. Soc.* **1986**, *108*, 5022–5024; c) X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2007**, *119*, 7815–7817; *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673; d) J. A. Kozak, G. R. Dake, *Angew. Chem.* **2008**, *120*, 4289–4291; *Angew. Chem. Int. Ed.* **2008**, *47*, 4221–4223; e) M. E. Jung, J. J. Chang, *Org. Lett.* **2010**, *12*, 2962–2965; f) Y.-R. Yang, Z.-W. Lai, L. Shen, J.-Z. Huang, X.-D. Wu, J.-L. Yin, K. Wei, *Org. Lett.* **2010**, *12*, 3430–3433; g) Y. Otsuka, F. Inagaki, C. Mukai, *J. Org. Chem.* **2010**, *75*, 3420–3426; h) Y.-R. Yang, L. Shen, J.-Z. Huang, T. Xu, K. Wei, *J. Org.*

Chem. **2011**, *76*, 3684 – 3690; i) H. Li, X. Wang, X. Lei, *Angew. Chem.* **2012**, *124*, 506 – 510; *Angew. Chem. Int. Ed.* **2012**, *51*, 491 – 495; j) G. Pan, R. M. Williams, *J. Org. Chem.* **2012**, *77*, 4801 – 4811; k) A. Nakayama, M. Kitajima, H. Takayama, *Synlett* **2012**, 2014 – 2024; l) N. Itoh, T. Iwata, H. Sugihara, F. Inagaki, C. Mukai, *Chem. Eur. J.* **2013**, *19*, 8665 – 8672.

[7] For recent select reports on the total synthesis of other fawcettimine-class *Lycopodium* alkaloids, see: a) A. Chandra, J. A. Pigza, J.-S. Han, D. Mutnick, J. N. Johnston, *J. Am. Chem. Soc.* **2009**, *131*, 3470 – 3471; b) A. Nakayama, N. Kogure, M. Kitajima, H. Takayama, *Org. Lett.* **2009**, *11*, 5554 – 5557; c) V. Bisai, R. Sarpong, *Org. Lett.* **2010**, *12*, 2551 – 2553; d) S. M. Canham, D. J. France, L. E. Overman, *J. Am. Chem. Soc.* **2010**, *132*, 7876 – 7877; e) J. Ramharter, H. Weinstabl, J. Mulzer, *J. Am. Chem. Soc.* **2010**, *132*, 14338 – 14339; f) X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, H. Shao, X. Meng, *Angew. Chem.* **2011**, *123*, 4002 – 4005; *Angew. Chem. Int. Ed.* **2011**, *50*, 3916 – 3919; g) A. Nakayama, N. Kogure, M. Kitajima, H. Takayama, *Angew. Chem.* **2011**, *123*, 8175 – 8178; *Angew. Chem. Int. Ed.* **2011**, *50*, 8025 – 8028; h) N. Shimada, Y. Abe, S. Yokoshima, T. Fukuyama, *Angew. Chem.* **2012**, *124*, 11994 – 11996; *Angew. Chem. Int. Ed.* **2012**, *51*, 11824 – 11826; i) H. M. Ge, L.-D. Zhang, R. X. Tan, Z.-J. Yao, *J. Am. Chem. Soc.* **2012**, *134*, 12323 – 12325; j) H. Zaimoku, H. Nishide, A. Nishibata, N. Goto, T. Taniguchi, H. Ishibashi, *Org. Lett.* **2013**, *15*, 2140 – 2143.

[8] a) R. G. Charles, *J. Org. Chem.* **1957**, *22*, 677 – 679; b) E. J. Corey, A. G. Myers, *J. Am. Chem. Soc.* **1985**, *107*, 5574 – 5576; c) T. R. Newhouse, P. S. J. Kaib, A. W. Gross, E. J. Corey, *Org. Lett.* **2013**, *15*, 1591 – 1593; d) M. D. Bel, A. Rovira, C. A. Guerrero, *J. Am. Chem. Soc.* **2013**, *135*, 12188 – 12191.

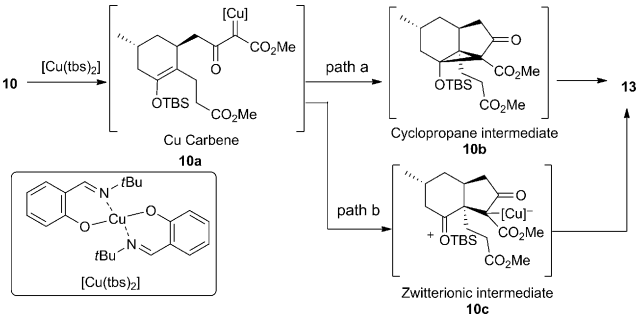
[9] The chiral enone **11** was obtained from (*R*)-(+)-pulegone in four steps as reported in Ref. [6d].

[10] H. M. L. Davies, G. Ahmed, M. R. Churchill, *J. Am. Chem. Soc.* **1996**, *118*, 10774 – 10782.

[11] Y. Liu, Y. Zhang, N. Jee, M. P. Doyle, *Org. Lett.* **2008**, *10*, 1605 – 1608.

[12] For reviews of the diazo compounds, see: a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; b) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577 – 6605.

[13] Proposed mechanism from **10** to **13**: The decomposition of diazo compound **10** induced by [Cu(tbs)$_2$] at 130 °C afforded Cu carbene **10a**, which reacted with the enol silyl ether moiety to give the intermediate **13** via the cyclopropane intermediate **10b** or the zwitterionic intermediate **10c**.



[14] a) J. Tsuji, *Acc. Chem. Res.* **1969**, *2*, 144 – 152; b) B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.* **1973**, *95*, 292 – 294.

[15] G. W. Kabalka, S. Yu, N.-S. Li, *Tetrahedron Lett.* **1997**, *38*, 5455 – 5458.

[16] a) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551 – 2651; b) Z. Xu, Q. Wang, J. Zhu, *Angew. Chem.* **2013**, *125*, 3354 – 3358; *Angew. Chem. Int. Ed.* **2013**, *52*, 3272 – 3276.

[17] CCDC 940353 (**16**), 937771 (**1**), 940354 (**21**), and 940355 (thiolactam of **20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] a) S. Grecian, J. Aubé in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, UK, **2009**, pp. 439 – 469; b) P. Feng, Y. Fan, F. Xue, W. Liu, S. Li, Y. Shi, *Org. Lett.* **2011**, *13*, 5827 – 5829.

[19] Regioselectivity was determined by using ^{1}H NMR spectroscopy.

[20] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011 – 1013.

[21] T. Mukaiyama, J.-I. Matsuo, H. Kitagawa, *Chem. Lett.* **2000**, 1250 – 1251.

[22] R. L. Beingessner, J. A. Farand, L. Barriault, *J. Org. Chem.* **2010**, *75*, 6337 – 6346.

[23] P. A. Grieco, Y. Yokoyama, G. P. Withers, F. J. Okuniewicz, C. L. J. Wang, *J. Org. Chem.* **1978**, *43*, 4178 – 4182.

[24] a) G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449 – 10459; b) S. Grecian, J. Aubé in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, UK, **2009**, pp. 191 – 237.

[25] For more details, see the Supporting Information.

[26] J. Chen, J. Chen, Y. Xie, H. Zhang, *Angew. Chem.* **2012**, *124*, 1048 – 1051; *Angew. Chem. Int. Ed.* **2012**, *51*, 1024 – 1027.

[27] K. Katakawa, M. Kitajima, N. Aimi, H. Seki, K. Yamaguchi, K. Furihata, T. Harayama, H. Takayama, *J. Org. Chem.* **2005**, *70*, 658 – 663.

[28] T. Honda, *Heterocycles* **2011**, *83*, 1 – 46.

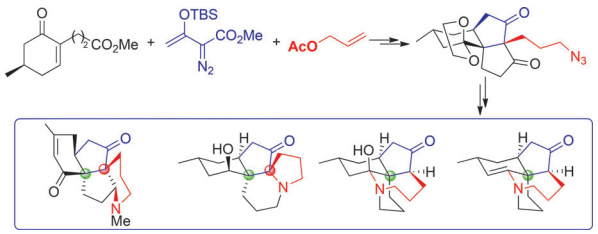
[29] For selected recent work on the divergent synthesis of natural products, see: a) A. N. Flyer, C. Si, A. G. Myers, *Nat. Chem.* **2010**, *2*, 886 – 892; b) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183 – 188; c) M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, *134*, 8078 – 8081.

Communications

Natural Product Synthesis

S.-H. Hou, Y.-Q. Tu,* L. Liu, F.-M. Zhang, S.-H. Wang,* X.-M. Zhang ——— ■■■■–■■■■

Divergent and Efficient Syntheses of the *Lycopodium* Alkaloids (−)-Lycojaponicumin C, (−)-8-Deoxyserratinine, (+)-Fawcettimine, and (+)-Fawcettidine



Four from one: The four title alkaloids (structures shown in blue box) have been synthesized by using a common versatile intermediate with a 6/5/5 tricyclic skeleton. This tricyclic intermediate could be easily assembled by using an intramolecular carbene addition/cyclization and a Dieckmann condensation/Tsuji–Trost allylation as key steps.