Total Synthesis

International Edition: DOI: 10.1002/anie.201610021
German Edition: DOI: 10.1002/ange.201610021

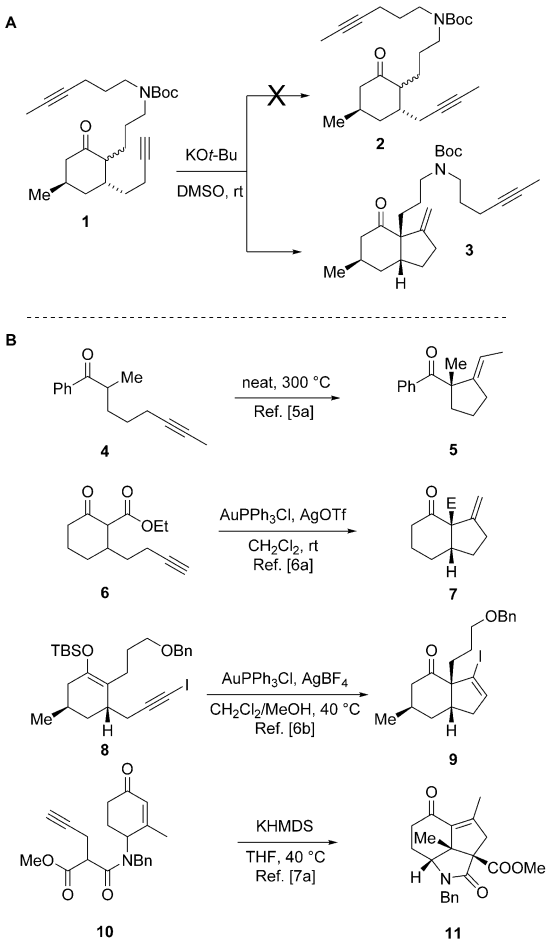
# A Conia-Ene-Type Cyclization under Basic Conditions Enables an Efficient Synthesis of (−)-Lycoposerramine R

*Felix W. W. Hartrampf, Takayuki Furukawa, and Dirk Trauner**

***Abstract:*** *An enantioselective total synthesis of the Lycopodium alkaloid lycoposerramine R is presented. It relies on a base-mediated cyclization that resembles the Conia-ene reaction of ynones and gold-catalyzed variants thereof. Thus, hydrindanones and other functionalized ring systems bearing an exocyclic alkene can be rapidly accessed at room temperature without noble metal catalysis or substrate preactivation.*

Carbon–carbon triple bonds combine high enthalpies of formation and low steric hindrance with remarkable kinetic inertness, which can be overcome, however, though appropriate activation. As such, they are very useful functional groups for the construction of complex molecular frameworks in multistep syntheses.[1] Indeed, alkynes have seen increasing use in synthesis, fueled by the development of transition-metal-catalyzed reactions that rely on the π-acidity of metals such as gold and platinum.[2] Recently, alkyne metathesis reactions and stereoselective *trans*-additions to alkynes have further increased the synthetic value of these venerable functional groups.[3]

Although their chemistry is now well developed, alkynes are occasionally found to react in unintended ways. During our studies towards the synthesis of lycopodine-type *Lycopodium* alkaloids, we sought to transform a terminal alkyne into an internal one under basic conditions.[4] To this end, we treated compound **1** with three equivalents of potassium *tert*-butoxide in dimethyl sulfoxide and observed a clean reaction that went to completion within 30 minutes. The product, however, turned out to be *cis*-hydrindane **3** bearing an *exo*-methylene group instead of the intended internal alkyne **2** (Scheme 1 A). In essence, this cyclization represents a variant of the classic thermal Conia-ene reaction discovered in the 1970s (Scheme 1 B).[5] This reaction occurs only under harsh thermal conditions (250–400 °C) due to the unfavorable equilibrium between the keto and enol tautomers. More recently, gold-catalyzed versions have emerged that require additional activation as a β-keto ester (**6**→**7**) or a silyl enol ether (**8**→**9**).[6] Reports on transition metal free, base-mediated carbocyclizations using unactivated alkynes are rare, with the notable exception of Dixon's study on *Daphniphyllum* alkaloids (**10**→**11**) and earlier work by Taguchi involving malonates.[7] This prompted us to investigate our cyclization more systematically. We were also well aware that hydrindanes such as **3** would be of great interest for the synthesis of *Lycopodium* alkaloids, especially of the fawcettimine subclass.[8]



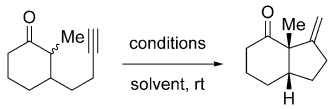

***Scheme 1.*** Reaction discovery and previous related examples.

To identify the best conditions for the cyclization we chose ynone **12** as a model substrate. A screen of different bases in DMSO showed that potassium *tert*-butoxide was indeed the most efficient promoter of the reaction. Other bases such as potassium hydroxide, ethoxide, and hexamethyldisilazide provided the product in significantly lower yield (Table 1, entries 2–4) or gave rise to product mixtures. Other counterions proved inferior with respect to reaction times and yields

[*] F. W. W. Hartrampf, T. Furukawa, Prof. Dr. D. Trauner
Department of Chemistry
Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, 81377 München (Germany)
E-mail: dirk.trauner@lmu.de
T. Furukawa
Department of Applied Chemistry, Faculty of Engineering
Osaka University
Suita, Osaka 565-0871 (Japan)
Supporting information and the ORCID identification number for one of the authors of this article can be found under http://dx.doi.org/10.1002/anie.201610021.

***Table 1:*** Reaction development.




**12** **13**

| Entry | Base | Equiv. | Solvent | Reaction time [h] | NMR yield [%][a] |
|---|---|---|---|---|---|
| **1** | **KO*t*-Bu** | **1.0** | **DMSO** | **0.5** | **71 (65)** |
| 2 | KOEt | 1.0 | DMSO | 0.5 | 65 |
| 3 | KOH | 1.0 | DMSO | 24 | 3 |
| 4 | KHMDS | 1.0 | DMSO | 5 | 57 |
| 5 | NaO*t*-Bu | 1.0 | DMSO | 2 | 47 |
| 6 | LiO*t*-Bu | 1.0 | DMSO | 16 | 0 |
| 7 | KO*t*-Bu | 0.2 | DMSO | 16 | 69 |
| 8 | KO*t*-Bu[b] | 0.2 | DMSO | 3 | 66 |
| 9 | KO*t*-Bu | 3.0 | DMSO | 0.5 | 56 |
| 10 | KO*t*-Bu | 1.0 | DMF | 16 | 18 |
| 11 | KO*t*-Bu | 3.0 | THF | 24 | 4 |
| 12 | KO*t*-Bu | 1.0 | THF/DMSO (1:1) | 1 | 70 |
| 13 | KO*t*-Bu[c] | 1.0 | THF | 16 | 6 |

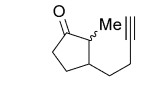
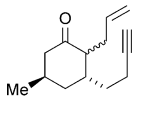
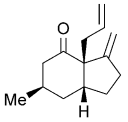
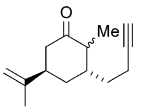
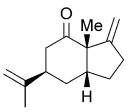
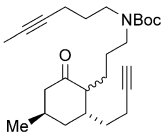
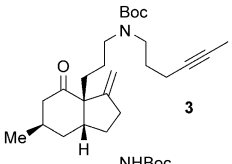
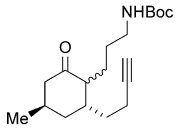
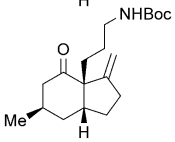
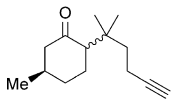
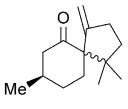
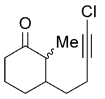
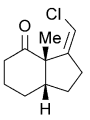
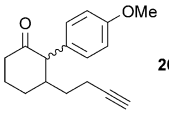
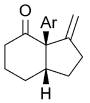
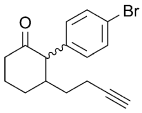
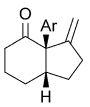
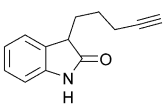
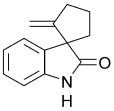
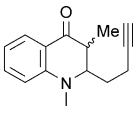
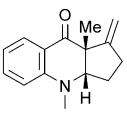
[a] Yield of isolated product in brackets. [b] 0.2 equiv. 18-crown-6 was added. [c] 3.0 equiv. DMSO was added.

(entries 5 and 6), as did other solvents or solvent mixtures (entries 10–13). Substoichiometric amounts of base also led to clean product formation but did not improve the yields. The addition of 18-crown-6 improved the rate, but had little if any effect on the yield. Under all conditions surveyed, the *cis*-hydrindane **13** was the only diastereomer observable by $^1$H NMR spectroscopy. To exclude possible catalysis from trace metals contained in the reagent or the substrate prepared via cuprate addition, we confirmed the absence of all metals commonly used in alkyne activation by ICP-AES.

With optimal conditions identified, we set out to investigate the scope and limitations of our method with a variety of substrates (Table 2). We typically used one equivalent of KO*t*-Bu in each case since it provided the cleanest reaction profile, unless stated otherwise. Cyclic ketones bearing various α-alkyl groups could be cyclized to afford compounds bearing a quaternary stereocenter (entries 1–5). As demonstrated in entries 4 and 5, both tertiary and secondary carbamates are tolerated. As an example of a nonterminal alkyne, alkynyl chloride **24** could be converted to the synthetically useful vinyl chloride **25**, which was obtained exclusively as the *cis* isomer. This matches Taguchi's analogous cyclization involving malonates.[7b]

By substituting α-alkyl for α-aryl groups, benzylic quaternary stereocenters could be furnished as well (entries 8 and 9). Frameworks other than hydrindanes could also be accessed, such as the spiro compounds **23** and **31**. Notably, the pulegone-derived alkyne **22** cyclized smoothly to establish two adjacent quaternary carbons (entry 6) in good yield. We were also able to expand our method to heterocyclic systems. Oxindole **30** cleanly underwent the cyclization to give spiro compound **31**, whose single-crystal X-ray structure is shown in the Supporting Information. Tetrahydroquinolinone **32** was also a viable substrate, affording the functionalized tricycle **33**, albeit in moderate yield.

***Table 2:*** Substrate scope.

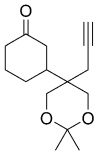
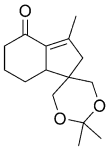
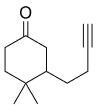
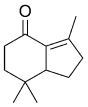
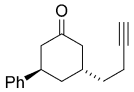
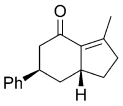
| Entry | Ynone | | Product | | Yield |
|---|---|---|---|---|---|
| 1 |  | **14** |  | **15** | 62% |
| 2 |  | **16** |  | **17** | 70% |
| 3 |  | **18** |  | **19** | 61% |
| 4 |  | **1** |  | **3** | 70% |
| 5 |  | **20** |  | **21** | 62% |
| 6 |  | **22** |  | **23** | 78% (1.3:1) |
| 7 |  | **24** |  | **25** | 65% |
| 8 |  | **26** |  | **27** | 28% |
| 9 |  | **28** |  | **29** | 52% |
| 10 |  | **30** |  | **31** | 75%[a] |
| 11 |  | **32** |  | **33** | 40% |

[a] 2.0 equiv. KO*t*-Bu was used. [b] NMR yield, preferably isolated as the Boc-protected oxindole. See the Supporting Information for details.

The reaction also worked well when cyclic ketones without α-substituents were used. In this case, the exocyclic double bonds isomerized under the basic conditions to yield conjugated enones, as had been observed previously by Dixon (Table 3).[7a] Overall, this transformation is reminiscent of an

***Table 3:*** Cyclization with concomitant double bond isomerization.

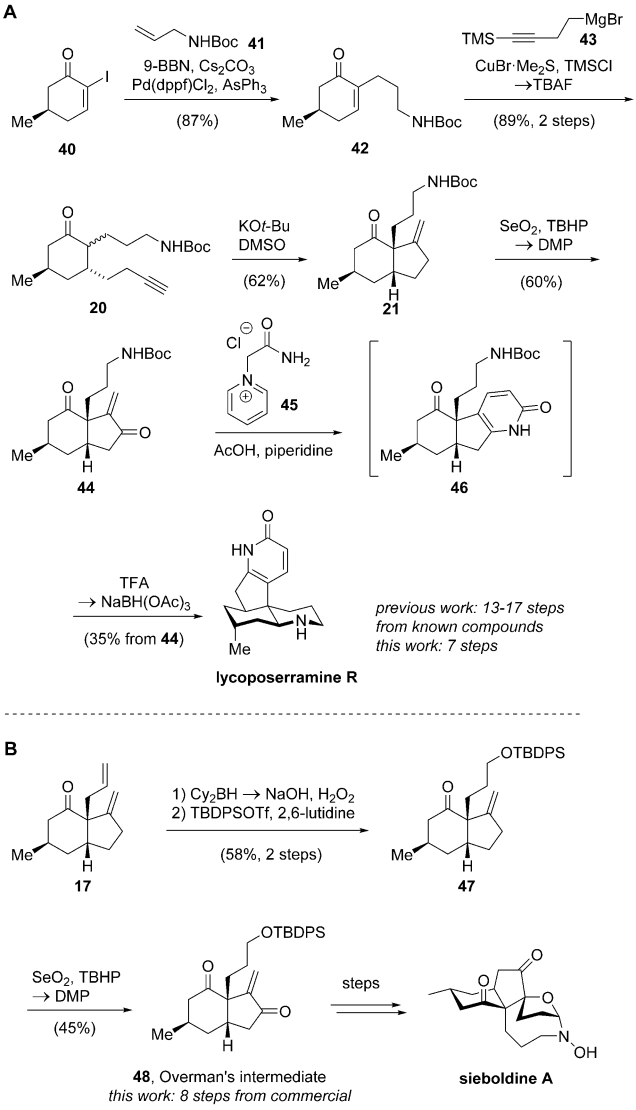
| Entry | Ynone | | Product | | Yield |
|---|---|---|---|---|---|
| 1 |  | **34** |  | **35** | 81%[a] |
| 2 |  | **36** |  | **37** | 52% |
| 3 |  | **38** |  | **39** | 62% |

[a] 4:1 mixture of *exo*/*endo* isomers favoring the enone.

intramolecular aldol condensation, but it can be carried out with acid-sensitive substrates such as **34**.

With the insight gained from these substrates, we returned to our initial goal of developing a short synthesis of *Lycopodium* alkaloids. We deemed our hydrindanone synthesis well suited to access the fawcettimine family, in particular lycoposerramine R. This tetracyclic alkaloid, which bears four stereocenters including a quaternary one, was isolated by Takayama and co-workers from *Lycopodium serratum* in 2009.[9] Due to its rather unusual structure, which also features an α-pyridone, it has attracted significant synthetic interest.[10] This has so far resulted in racemic syntheses by the Sarpong[10a] and Takayama[10b] groups as well as an enantioselective synthesis by the latter.[10c] The key quaternary stereocenter was set by Eschenmoser–Claisen, Diels–Alder, and alkylation reactions, respectively, in these studies. The total number of steps ranged from 13 for the shortest racemic synthesis to 17 for the enantioselective synthesis. We reasoned that our method would allow for a more rapid enantioselective synthesis starting from α-iodo ketone **40**, a popular building block in the synthesis of *Lycopodium* alkaloids.[11] Our synthesis began with a *B*-alkyl Suzuki reaction of *N*-Boc-allylamine (**41**) and iodoenone **40**, delivering enone **42** in high yield.[12] Cuprate addition of the known Grignard reagent **43** proceeded as planned, yielding the cyclization precursor **20** in very high overall yield after double desilylation (Scheme 2).

The ensuing cyclization furnished the desired hydrindanone **21** in 62% yield. Allylic oxidation of **21** to enone **44** could be carried out in a one-pot procedure using $SeO_2$/TBHP, followed by Dess–Martin oxidation. The transformation of the enone into an α-pyridone proved to be quite challenging due to competing decomposition under a variety of conditions.[13] Eventually, a modification of the classic Kröhnke reaction gave the desired pyridone: heating enone **44** with acetamide derivative **45** for an extended time and at elevated temperature provided **46**, which was used directly in the ensuing steps.[14] A Boc carbamate deprotection followed




***Scheme 2.*** A) Total synthesis of lycoposerramine R; B) Synthesis of Overman's sieboldine A intermediate. See the Supporting Information for detailed procedures.

by reductive amination could be carried out as a one-pot procedure to give lycoposerramine R as a single diastereomer in 35% overall yield from enone **44**. Our synthetic compound was identical in all respects with the natural material isolated by Takayama.[9] The key disconnection also proved useful in the synthesis of hydrindanone **17**, obtained with a route similar to **21**. Compound **17** was readily converted into enone **48** in three steps via hydrindanone **47**. This allowed us to intercept Overman's elegant route to sieboldine A,[15] which hinges on Prins pinacol chemistry to furnish the hydrindane.[16] With our route, intermediate **48** can be accessed in 8 steps from commercial starting materials, which compares favorably with the 16 steps of the original route.

In summary, a convenient base-mediated cyclization has been developed that gives access to useful polycyclic building blocks. The reaction is particularity well-suited for the construction of quaternary stereocenters next to carbonyl groups in a variety of ring systems. Notably, it occurs at room

temperature without the need for preactivation of the substrate or transition metal catalysis. The exact mechanism of this reaction remains to be determined and will be the subject of detailed analysis, both on the theoretical and the experimental level. We have successfully applied our methodology to the synthesis of lycoposerramine R, resulting in the most concise asymmetric synthesis to date (7 steps from a known iodoenone). In addition, an intermediate of Overman's sieboldine A synthesis was obtained, shortening the sequence significantly. Applications of this chemistry to the synthesis of other alkaloids are under investigation and will be reported in due course.

## Acknowledgements

We thank Giulio Volpin, Nina Vrielink, Benjamin Williams, Dr. Bryan Matsuura and Dr. Hong-Dong Hao for helpful discussions during the preparation of this manuscript. We acknowledge Stephan Heß and Christian Steinborn for experimental assistance and JSPS for a JSPS Research Fellowship for Young Scientists for T. Furukawa.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** alkynes · Conia-ene reaction · hydrindanes · lycopodium alkaloids · total synthesis

[1] a) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.* **2011**, *111*, 2937 – 2980; b) U. Wille, *Chem. Rev.* **2013**, *113*, 813 – 853.

[2] a) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269 – 2281; b) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028 – 9072.

[3] a) A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794 – 2819; *Angew. Chem.* **2013**, *125*, 2860 – 2887; b) S. M. Rummelt, K. Radkowski, D.-A. Roşca, A. Fürstner, *J. Am. Chem. Soc.* **2015**, *137*, 5506 – 5519; c) B. M. Trost, Z. T. Ball, *Synthesis* **2005**, 853 – 887.

[4] J. Chan, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 10682 – 10691.

[5] a) R. Bloch, P. Le Perchec, F. Rouessac, J. M. Conia, *Tetrahedron* **1968**, *24*, 5971 – 5989; b) J. M. Conia, P. Le Perchec, *Synthesis* **1975**, *1975*, 1 – 19.

[6] a) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526 – 4527; b) S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem. Int. Ed.* **2006**, *45*, 5991 – 5994; *Angew. Chem.* **2006**, *118*, 6137 – 6140; c) D. Hack, M. Blumel, P. Chauhan, A. R. Philipps, D. Enders, *Chem. Soc. Rev.* **2015**, *44*, 6059 – 6093; for a related enamide cyclization in total synthesis, see: d) J. A. Kozak, G. R. Dake, *Angew. Chem. Int. Ed.* **2008**, *47*, 4221 – 4223; *Angew. Chem.* **2008**, *120*, 4289 – 4291.

[7] a) C. Kourra, F. Klotter, F. Sladojevich, D. J. Dixon, *Org. Lett.* **2012**, *14*, 1016 – 1019; b) O. Kitagawa, T. Suzuki, H. Fujiwara, M. Fujita, T. Taguchi, *Tetrahedron Lett.* **1999**, *40*, 4585 – 4588; for other base-mediated reactions using alkynes, see: c) C. Koradin, A. Rodriguez, P. Knochel, *Synlett* **2000**, 1452 – 1454; d) K. Gao, J. Wu, *Org. Lett.* **2008**, *10*, 2251 – 2254; e) E. Dumez, A.-C. Durand, M. Guillaume, P.-Y. Roger, R. Faure, J.-M. Pons, G. Herbette, J.-P. Dulcère, D. Bonne, J. Rodriguez, *Chem. Eur. J.* **2009**, *15*, 12470 – 12488; f) S.-R. Li, C.-J. Shu, L.-Y. Chen, H.-M. Chen, P.-Y. Chen, E.-C. Wang, *Tetrahedron* **2009**, *65*, 8702 – 8707; g) B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova, I. A. Ushakov, *J. Org. Chem.* **2012**, *77*, 6880 – 6886; h) B. A. Trofimov, E. Y. Schmidt, I. A. Ushakov, N. V. Zorina, E. V. Skital'tseva, N. I. Protsuk, A. b. I. Mikhaleva, *Chem. Eur. J.* **2010**, *16*, 8516 – 8521; i) J. Weng, Y. Chen, B. Yue, M. Xu, H. Jin, *Eur. J. Org. Chem.* **2015**, 3164 – 3170.

[8] R. A. Murphy, R. Sarpong, *Chem. Eur. J.* **2014**, *20*, 42 – 56.

[9] K. Katakawa, N. Kogure, M. Kitajima, H. Takayama, *Helv. Chim. Acta* **2009**, *92*, 445 – 452.

[10] a) V. Bisai, R. Sarpong, *Org. Lett.* **2010**, *12*, 2551 – 2553; b) H. Ishida, S. Kimura, N. Kogure, M. Kitajima, H. Takayama, *Tetrahedron* **2015**, *71*, 51 – 56; c) H. Ishida, S. Kimura, N. Kogure, M. Kitajima, H. Takayama, *Org. Biomol. Chem.* **2015**, *13*, 7762 – 7771.

[11] a) D. Caine, K. Procter, R. A. Cassell, *J. Org. Chem.* **1984**, *49*, 2647 – 2648; b) T. L. Scott, B. C. G. Söderberg, *Tetrahedron* **2003**, *59*, 6323 – 6332; c) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jorgensen, *Chem. Commun.* **2006**, 4928 – 4930.

[12] a) B. M. Trost, C. B. Lee, *J. Am. Chem. Soc.* **1998**, *120*, 6818 – 6819; for a review on B-alkyl Suzuki couplings, see: b) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544; *Angew. Chem.* **2001**, *113*, 4676.

[13] a) T. Koshiba, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2009**, *11*, 5354 – 5356; b) M. Fujii, T. Nishimura, T. Koshiba, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2013**, *15*, 232 – 234; c) T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2013**, *135*, 3243 – 3247; d) R. Khajuria, P. Kannaboina, K. K. Kapoor, A. Gupta, G. Raina, A. K. Jassal, L. K. Rana, M. S. Hundal, P. Das, *Org. Biomol. Chem.* **2015**, *13*, 5944 – 5954; e) R. Boobalan, C. Chen, *Tetrahedron Lett.* **2016**, *57*, 1930 – 1934.

[14] Y. Besidsky, K. Luthman, A. Claesson, C. J. Fowler, I. Csoregh, U. Hacksell, *J. Chem. Soc. Perkin Trans. 1* **1995**, 465 – 474.

[15] Y. Hirasawa, H. Morita, M. Shiro, J. i. Kobayashi, *Org. Lett.* **2003**, *5*, 3991 – 3993.

[16] a) S. M. Canham, D. J. France, L. E. Overman, *J. Am. Chem. Soc.* **2010**, *132*, 7876 – 7877; b) S. M. Canham, D. J. France, L. E. Overman, *J. Org. Chem.* **2013**, *78*, 9 – 34; for a different rearrangement-based approach towards sieboldine A, see: c) X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, H. Shao, X. Meng, *Angew. Chem. Int. Ed.* **2011**, *50*, 3916 – 3919; *Angew. Chem.* **2011**, *123*, 4002 – 4005; d) X.-M. Zhang, H. Shao, Y.-Q. Tu, F.-M. Zhang, S.-H. Wang, *J. Org. Chem.* **2012**, *77*, 8174 – 8181.

Manuscript received: October 13, 2016
Final Article published: ■■ ■■, ■■■■

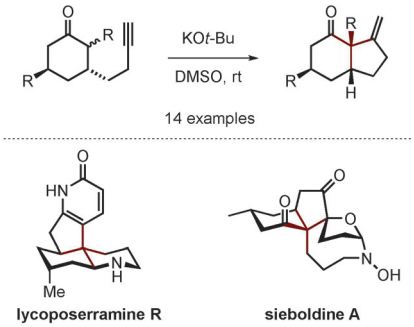
  

# Communications

## Total Synthesis

F. W. W. Hartrampf, T. Furukawa, D. Trauner* ——— ■■■■–■■■■

A Conia-Ene-Type Cyclization under Basic Conditions Enables an Efficient Synthesis of (−)-Lycoposerramine R




**An enantioselective total synthesis** of the *Lycopodium* alkaloid lycoposerramine R relies on a base-mediated cyclization that resembles the Conia-ene reaction of ynones and gold-catalyzed variants thereof. Thus, hydrindanones and other functionalized ring systems bearing an *exo*-methylene group can be rapidly accessed at room temperature without noble metal catalysis or substrate preactivation.