Total Synthesis

International Edition: DOI: 10.1002/anie.201508996
German Edition: DOI: 10.1002/ange.201508996

Collective Total Syntheses of Atisane-Type Diterpenes and Atisine-Type Diterpenoid Alkaloids: (±)-Spiramilactone B, (±)-Spiraminol, (±)-Dihydroajaconine, and (±)-Spiramines C and D

Hang Cheng, Fan-Hao Zeng, Xue Yang, Yin-Juan Meng, Liang Xu, and Feng-Peng Wang*

Dedicated to Professor Guo-Qiang Lin

Abstract: *The first total syntheses of the architecturally complex atisane-type diterpenes and biogenetically related atisine-type diterpenoid alkaloids (±)-spiramilactone B, (±)-spiraminol, (±)-dihydroajaconine, and (±)-spiramines C and D are reported. Highlights of the synthesis include a late-stage biomimetic transformation of spiramilactone B, a facile formal lactone migration from the pentacyclic skeleton of spiramilactone E, a highly efficient and diastereoselective 1,7-enyne cycloisomerization to construct the functionalized tetracyclic atisane skeleton, and a tandem retro-Diels–Alder/intramolecular Diels–Alder sequence to achieve the tricyclo-[6.2.2.0] ring system.*

Atisine-type diterpenoid alkaloids and atisane-type diterpenes are widely distributed in the plant world and have long been attractive targets for synthetic chemists because of their physiological and architectural properties.[1] Spiramines C and D (**1**, **2**; Figure 1), representative alkaloids for the *Spiraea japonica* complex, were first isolated by Hao and co-workers in 1987.[2] These compounds and their derivatives have been shown to exhibit anti-platelet aggregation, anti-inflammatory, and neuroprotective effects,[3a,b] and are capable of inhibiting Wnt/β-catenin signaling and colon-cancer-cell tumorigenesis.[3c–e] The structures of spiramines C and D show an unprecedentedly complex heptacyclic ring framework that contains three bridged ring units (A/E, B/F, and C/D). One of the distinctive structural characteristics of spiramines C and D is a C7–C20 oxygen-bridge linkage that distinguishes them from other atisine-type members, such as isoatisine (**4**) and dihydroajaconine (**3**).[4] This unusual structural motif is also found in a few members of the atisane-type diterpenes, such as spiraminol (**5**)[5a] and spiramilactone B (**6**),[5b] which surprisingly were isolated from the same *Spiraea* plants. Compounds **5** and **6** are closely related to spiramines C and D and only differ in the constitution of ring E. It has been proven that spiraminol (**5**) can be transformed into spiramines C and D by reaction with ethanolamine, indicating that the spiraminol could be regarded as the potential biosynthetic precursor of *Spiraea* alkaloids.[3a,6]

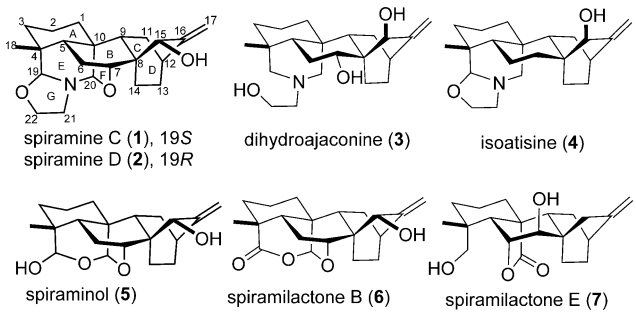


Figure 1. Representative members of the series of atisane-type diterpenes and atisine-type diterpenoid alkaloids.

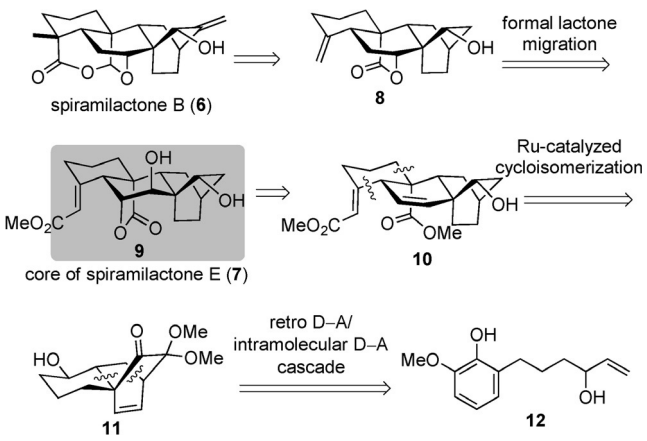
Despite the intriguing biosynthetic and structural properties of these *Spiraea* atisine-type alkaloids and related diterpenes, there are no reports on their total syntheses. To date, successful total syntheses towards atisane diterpenes and atisine diterpenoid alkaloids have been limited to some relatively uncomplicated compounds, such as methyl atisenoate,[7a–d] antiquorin,[7e] atisine or isoatisine (**4**),[7d,f–k] and azitine.[7l] In continuation of our long-standing interest in the chemistry of diterpenoid alkaloids,[8] we wish to describe herein the first total syntheses of several atisane- and atisine-type compounds with more highly oxidized skeletons including spiramilactone B (**6**), spiraminol (**5**), spiramines C and D (**1**,**2**), and dihydroajaconine (**3**), using a unified synthetic strategy that is distinctly different from previous approaches.

In view of the chemical and biogenetic relationships of atisine-type diterpenoid alkaloids and atisane-type diterpenes proposed by Hao and co-workers,[3a,b] it is obvious that spiramines C and D could be generated from spiramilactone B (**6**) via spiraminol (**5**) by a biomimetic reduction of the lactone group followed by condensation with ethanolamine.[6] Moreover, reduction of the C15-OH epimer of spiramines C and D would deliver dihydroajaconine (**3**).

Thus, spiramilactone B (**6**) was chosen as the first natural product target in our synthetic route. By retrosynthetic analysis (Scheme 1), we envisioned that hexacyclic **6** could be formed from the pentacyclic δ-lactone **8**, which might be generated by a formal lactone migration[9] from the γ-lactone **9**. Interestingly, the pentacyclic core structure of **9** is common to another naturally occurring atisane diterpene named

[*] H. Cheng, F.-H. Zeng, X. Yang, Y.-J. Meng, Prof. L. Xu, Prof. F.-P. Wang
Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education, West China School of Pharmacy and State Key Laboratory of Biotherapy, Sichuan University
Chengdu 610041 (P. R. China)
E-mail: liangxu@scu.edu.cn

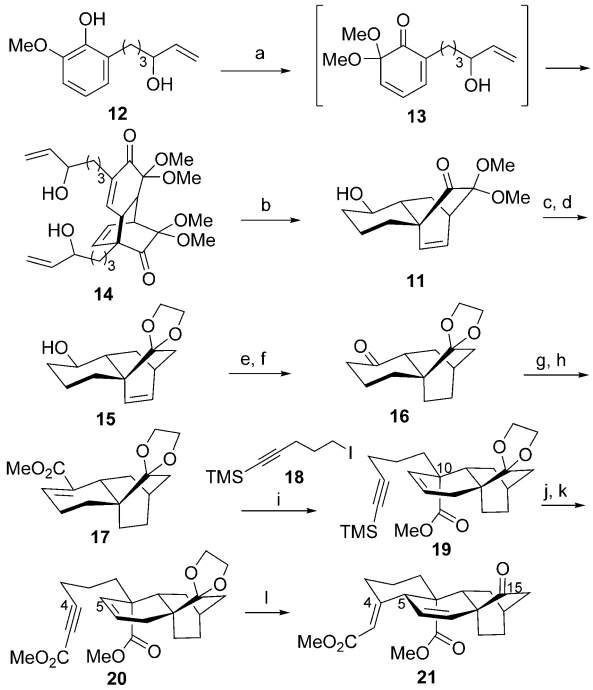
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508996.



Scheme 1. Retrosynthetic analysis of spiramilactone B (**6**). D–A = Diels–Alder.

spiramilactone E (**7**; Figure 1).[10] Subsequently, the bridged γ-lactone **9** could be prepared from the functionalized tetracyclic atisane skeleton **10**, which itself could be formed by installation of the *trans*-fused ring A by using a pivotal ruthenium-catalyzed cycloisomerization reaction[11] on the tricyclic intermediate **11**. In turn, **11** could be obtained by means of an oxidative dearomatization of phenol **12** followed by intramolecular Diels–Alder reaction developed previously by us and Liao and co-workers.[8b,12]

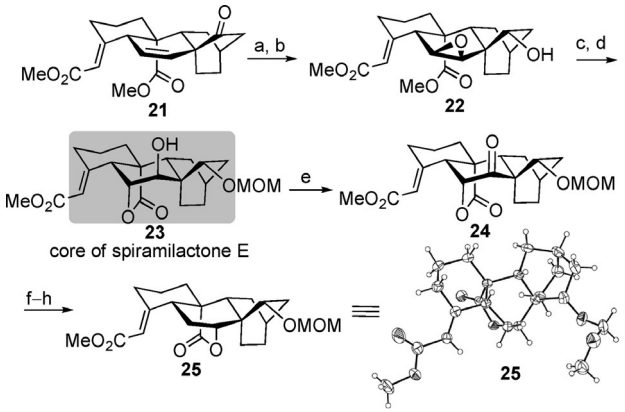
Our synthetic efforts commenced with the preparation of the required tricyclic intermediate **11** with an optimized procedure based on a previously reported method.[12] As shown in Scheme 2, dearomatization of the readily available phenol **12**[8b] with $PhI(OAc)_2$ in MeOH at room temperature generated masked *ortho*-benzoquinone **13** which dimerized spontaneously to **14**.[12] Upon heating **14** to reflux in mesitylene, a retro Diels–Alder/intramolecular Diels–Alder cascade process proceeded efficiently to give the desired cycloadduct **11** as a single diastereomer in 86% yield over two steps. Notably, by using this improved reaction sequence, **11** could be efficiently and reliably accessed on the decagram scale from **12**. With the tricyclo[6.2.2.0] ring precursor **11** in hand, the installation of *trans*-fused six-membered ring A was next addressed (Scheme 2). After sequential reductive removal of the two methoxy groups of **11** with SmI_2[13] and protection of the ketone with glycol alcohol, oxidation of the hydroxy group of the resulting ethylene ketal **15** with Dess–Martin periodinane (DMP)[14] followed by hydrogenation of the double bond afforded ketone **16** in 57% overall yield. Subsequently, vinyl triflate formation[15] followed by palladium-catalyzed carboxymethylation[16] converted ketone **16** into α,β-unsaturated methyl ester **17** in 75% yield. Moving forward, the elaboration of the requisite side-chain for eventual construction of ring A called for a stereoselective alkylation occurring at the C10 position in enoate **17** to an *exo* orientation. To our delight, the deconjugative alkylation[17] of **17** was effected on treatment with LDA/DMPU (LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) then iodide derivative **18**, delivering the desired **19** as a single diastereomer in 75% yield. The exclusive stereochemistry of alkylation could



Scheme 2. Construction of the functionalized tetracyclic atisane skeleton **21**. Reagents and conditions: a) $PhI(OAc)_2$, MeOH, RT, 2 h, 95%; b) mesitylene, reflux, 3 h, 91%; c) SmI_2, THF/MeOH (5:1 v/v), RT, 5 h, 72%; d) $(CH_2OH)_2$, CAS (5 mol%), toluene, reflux, 5 h, 90%; e) DMP, Na_2CO_3, CH_2Cl_2, 0°C to RT, 2 h, 92%; f) H_2, 10% Pd/C, MeOH, 30°C, 4 h, 96%; g) NaHMDS, Tf_2NPh, THF, −78°C, 3 h; h) $[Pd(PPh_3)_4]$, Et_3N, CO, MeOH/DMF (2:3 v/v), 70°C, 10 h, 89% over two steps; i) LDA, DMPU, **18**, THF, 0°C, 3.5 h, 75%; j) K_2CO_3, MeOH, RT, 2 h, 95%; k) *n*BuLi, $ClCO_2Me$, THF, −78°C to 0°C, 1.5 h, 83%; l) $[CpRu(CH_3CN)_3]PF_6$ (10 mol%), DMF, acetone, RT, 1 h; then TsOH, RT, 1 h, 91%. CAS = L(−)-camphorsulfonic acid; DMP = Dess–Martin periodinane; NaHMDS = sodium bis(trimethylsilyl)amide; Tf = trifluoromethanesulfonyl; TsOH = *p*-toluenesulfonic acid; DMF = *N*,*N*-dimethylformamide; LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; Cp = cyclopentadienyl.

be attributed to the relatively more congested *endo*-side of the allylic ester anion. Subsequent desilylation followed by a straightforward acylation furnished the enyne ester **20**, setting the stage for the crucial Ru-catalyzed cycloisomerization. Gratifyingly, with a slightly modified version of the conditions of Trost et al.,[11] 1,7-enyne cycloisomerization of **20** by employing 10 mol% $[CpRu(CH_3CN)_3]PF_6$ in the presence of 1.5 equivalents of DMF as additive, followed by removal of the ethylene ketal group in a one-pot step, proceeded efficiently to furnish the tetracyclic ketone **21** as a single diastereomer in excellent yield.

With the functionalized tetracyclic atisene skeleton in hand, the next challenging task was to install the bridged lactone moieties on the molecules. As shown in Scheme 3, stereoselective reduction of ketone **21** with Super-Hydride ($LiBHEt_3$) at −78°C followed by epoxidation of C6–C7 olefin using *m*-chloroperoxybenzoic acid (*m*-CPBA)[18] furnished **22** as the major hydroxy isomer. After protection of the hydroxy group of **22** with a methoxymethyl (MOM) group, regioselective ring-opening of the epoxide in the presence of the catalytic $[Ti(O\mathit{i}Pr)_2Cl_2]$ led to exclusive formation of the

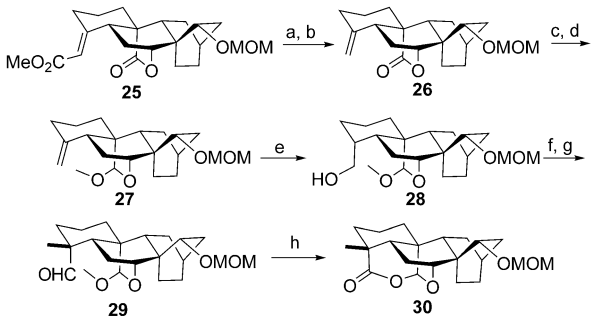


Scheme 3. Installation of the lactone moieties. Reagents and conditions: a) $LiBHEt_3$, THF, −78 °C, 30 min, 85%; b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 71%; c) MOMCl, iPr_2NEt, CH_2Cl_2, 0 °C, 3.5 h, 89%; d) $[Ti(OiPr)_2Cl_2]$, CH_2Cl_2, −20 °C, 1 h, 83%; e) DMP, $NaHCO_3$, CH_2Cl_2, RT, 1 h, 90%; f) SmI_2, THF/MeOH (10:1 v/v), −78 °C, 2 h; g) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF:MeOH (5:1 v/v), 1 h; h) DIC, HOBt, toluene, 45 °C, 3 h, 75% over three steps. *m*-CPBA = *m*-chloroperoxybenzoic acid; MOMCl = chloromethyl methyl ether; DIC = *N*,*N*′-diisopropylcarbodiimide; HOBt = 1-hydroxybenzotriazole.

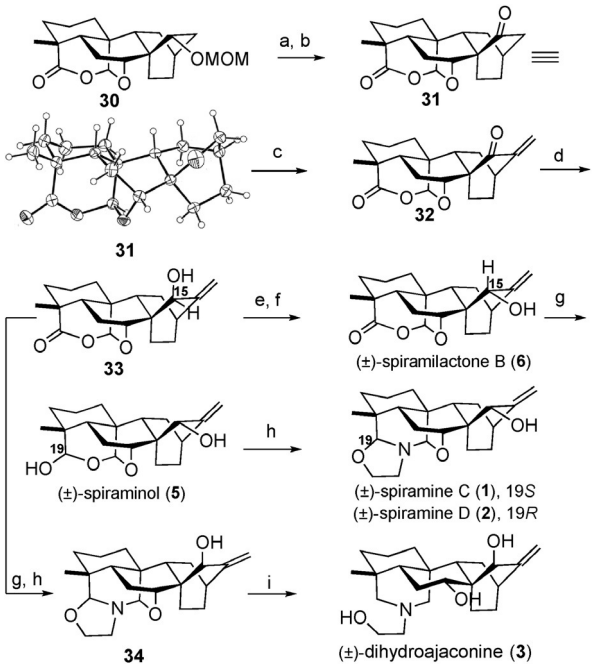
hydroxy γ-lactone **23**, completing the core pentacyclic structure of spiramilactone E (**7**). Next, the formal lactone migration from γ-lactone **23** to δ-lactone **25** was achieved by a straightforward four-step sequence.[19] First DMP oxidation of the hydroxy group of **23** gave ketone **24** in 90% yield, then sequential reductive α-deoxygenation of ketone **24** with SmI_2,[13] stereoselective reduction of the carbonyl group with $NaBH_4$, and lactonization of the resulting hydroxy acid with *N*,*N*′-diisopropylcarbodiimide and 1-hydroxybenzotriazole ultimately furnished the desired δ-lactone **25** (characterized by X-ray crystallography)[20] in 75% overall yield (over three steps). Notably, the crude acid intermediates in the reaction sequence could be directly used in the next steps without purification.

With the requisite pentacyclic lactone **25** in hand, we focused our attention on constructing the hexacyclic skeleton of spiramilactone B (Scheme 4). Ozonolysis of the conjugated enoate **25** followed by Takai olefination[21] of the resulting ketone using CH_2Br_2 in the presence of $TiCl_4$/Zn afforded terminal olefin **26** in 72% yield. Conversion of lactone **26** to aldolactol **27** was achieved in 85% yield by reduction with diisobutylaluminium hydride (DIBAL-H) followed by condensation with MeOH in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS). Hydroboration–oxidation[22] of olefin **27** gave the primary alcohol **28**. DMP oxidation of **28** afforded a labile aldehyde, which was immediately subjected to an exclusive alkylation on treatment with potassium *tert*-butoxide and methyl iodide, delivering the methyl group to the β-face to give **29** in 87% yield.[8d] Pleasingly, attempt to oxidize aldehyde to acid using Pinnick oxidation[23] resulted in direct formation of lactone **30** in 90% yield, completing the whole hexacyclic skeleton of spiramilactone B.

The synthetic steps involved in the final stage of the synthesis are summarized in Scheme 5. Removal of the MOM protecting group of **30** under mild conditions ($ZnBr_2$/*n*-PrSH)[24] followed by DMP oxidation of the resulting alcohol led cleanly to the ketone **31** (characterized by X-ray crystallography).[20] The subsequent Eschenmoser α-methe-



Scheme 4. Construction of the hexacyclic skeleton **30**. Reagents and conditions: a) O_3, CH_2Cl_2, −78 °C, 45 min, 95%; b) $PbCl_2$, Zn, $TiCl_4$, CH_2Br_2, THF/CH_2Cl_2 (5:2 v/v), 0 °C to RT, 2.5 h, 72%; c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; d) PPTS, MeOH, RT to 45 °C, 5 h, 85% over two steps; e) $BH_3{\cdot}Me_2S$ (1 M in THF), THF, 0 °C, 1 h; then 30% H_2O_2, 3 N NaOH, 30 min, 75%; f) DMP, $NaHCO_3$, CH_2Cl_2, RT, 1 h; g) *t*BuOK, CH_3I, −20 °C, 40 min; h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (3:1 v/v), −5 °C, 78% over three steps. DIBAL-H = diisobutylaluminium hydride; PPTS = pyridinium *p*-toluenesulfonate.



Scheme 5. Total syntheses of (±)-spiramilactone B (**6**), (±)-spiraminol (**5**), (±)-spiramines C and D (**1**,**2**), and (±)-dihydroajaconine (**3**). Reagents and conditions: a) CH_2Cl_2, $ZnBr_2$, *n*-PrSH, 3 h; b) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to RT, 1 h, 81% over two steps; c) LiHMDS, *N*,*N*-dimethylmethyleneiminium iodide, THF, −78 °C, 3.5 h; CH_3I, CH_2Cl_2, RT, 8 h; DBU, CH_2Cl_2, RT, 2 h, 71%; d) $NaBH_4$, MeOH/CH_2Cl_2 (2:1 v/v), −20 °C, 1 h, 95% (β:α = 5:1); e) PhSCl, Et_3N, Et_2O, 0 °C to RT, 1.5 h, 99%; f) $P(OMe)_3$, MeOH, 50 °C, 72 h, 64% (91% yield based on recovered **33**); g) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, 90% for **5**; h) $H_2N(CH_2)_2OH$, THF, reflux, 3 h; silica gel, MeOH, 8 h, 60% for (±)-spiramine C (**1**), 36% for (±)-spiramine D (**2**); i) $NaBH_4$, MeOH, RT, 5 h, 85% for three steps from **33**. DBU = 1.8-diazabicyclo-[5.4.0]undec-7-ene.

nylation of ketone **31** proceeded smoothly by means of a successive three-step sequence to provide exocyclic enone **32** in 71% yield.[25] However, for the synthesis of spiramilactone B, reduction of enone **32** with $NaBH_4$ unfortunately gave the undesired β-OH isomer **33** as the major product (β:α = 5:1). After an unsuccessful attempt to invert the configuration of the β-OH isomer with Mitsunobu reaction, the stereochemistry of the allylic alcohol of **33** was inverted, for the most part, by a Mislow–Evans rearrangement[26] via an allylic sulfoxide intermediate (see the Supporting Information for the detailed description), to provide (±)-spiramilactone B (**6**) in 64% yield (after separation and purification)). Next, reduction of the lactone moiety with DIBAL-H at −78 °C successfully gave (±)-spiraminol (**5**) as a single C-19 epimer,[27] which condensed with ethanolamine in THF to deliver (±)-spiramine C (**1**) and (±)-spiramine D (**2**) in 60% and 36% yield, respectively.[6] Additionally, another naturally occurring atisine-type diterpenoid alkaloid (±)-dihydroajaconine (**3**) bearing a C15 positioned β-OH group was smoothly synthesized by complete reduction of the C15-OH epimers **34** of spiramines C/D. Compound **34** itself was prepared by applying the same reduction/condensation sequence to epimer **33** of spiramilactone B.

In summary, we have achieved the collective total syntheses[28] of several members of the structurally complex atisane-type diterpenes and related atisine-type diterpenoid alkaloids, namely (±)-spiramilactone B, (±)-spiraminol, (±)-spiramines C and D, and (±)-dihydroajaconine, characterized by late-stage biomimetic transformations of (±)-spiramilactone B. The synthesis of spiramilactone B features the effective construction of the hexacyclic system from the pentacyclic core structure **23** of spiramilactone E by means of a straightforward formal lactone migration. In the construction of the pentacyclic skeleton of spiramilactone E bearing a γ-lactone moiety, a unique retro Diels–Alder/intramolecular Diels–Alder cascade sequence allowed rapid access to the tricyclo[6.2.2.0] ring system **11**. Subsequently, a diastereoselective Ru-catalyzed 1,7-enyne cycloisomerization was used to achieve the highly functionalized tetracyclic atisane skeleton **21**. Further development of the asymmetric synthetic route as well as application of this new strategy for construction of functionalized atisane skeletons to synthesize architecturally more complex hetidine- or hetisine-type diterpenoid alkaloids[1c] are currently underway in our laboratory.

Acknowledgements

Financial support for this work was provided by the National Natural Science Foundation of China (Grant Numbers 21472129 and 21272163).

Keywords: alkaloids · cycloisomerization · ruthenium · terpenoids · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 392–396
Angew. Chem. **2016**, *128*, 400–404

[1] a) A. M. Hamlin, J. K. Kisunzu, R. Sarpong, *Org. Biomol. Chem.* **2014**, *12*, 1846; b) G.-L. Zhu, R. Liu, B. Liu, *Synthesis* **2015**, *47*, 2691; c) F.-P. Wang, X.-T. Liang, in *The Alkaloids: Chemistry and Biology*, (Ed.: G. A. Cordell), Elsevier Science, New York, **2002**, Vol. 59, pp. 1–280.

[2] a) X.-J. Hao, M. Node, T. Taga, Y. Miwa, J. Zhou, S.-Y. Chen, K. Fuji, *Chem. Pharm. Bull.* **1987**, *35*, 1670; b) M. Node, X.-J. Hao, J. Zhou, S.-Y. Chen, T. Taga, Y. Miwa, K. Fuji, *Heterocycles* **1990**, *30*, 635.

[3] a) X.-J. Hao, Y.-M. Shen, L. Li, H.-P. He, *Curr. Med. Chem.* **2003**, *10*, 2253; b) X.-J. Hao, *Huaxue Jinzhan* **2009**, *21*, 84; c) C. Yan, L. Huang, H.-C. Liu, D.-Z. Chen, H.-Y. Liu, X.-H. Li, Y. Zhang, M.-Y. Geng, Q. Chen, X.-J. Hao, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1884; d) W. Wang, H.-Y. Liu, S. Wang, X.-J. Hao, L. Li, *Cell Res.* **2011**, *21*, 730; e) L. Zhao, F. He, H.-Y. Liu, Y.-S. Zhu, W.-L. Tian, P. Gao, H.-P. He, W. Yue, X.-B. Lei, B.-Y. Ni, X.-H. Wang, H.-J. Jin, X.-J. Hao, J.-L. Lin, Q. Chen, *J. Biol. Chem.* **2012**, *287*, 1054.

[4] S. W. Pelletier, R. S. Sawhney, N. V. Mody, *Heterocycles* **1978**, *9*, 1241.

[5] a) X.-J. Hao, J. Zhou, K. Fuji, M. Node, *Chin. Chem. Lett.* **1992**, *3*, 427; b) J.-L. Nie, X.-J. Hao, *Acta Botanica Yunnanica* **1996**, *18*, 226.

[6] P.-J. Zhao, S. Gao, L.-M. Fan, J.-L. Nie, H.-P. He, Y. Zeng, Y.-M. Shen, X.-J. Hao, *J. Nat. Prod.* **2009**, *72*, 645.

[7] a) M. Toyota, T. Wada, K. Fukumoto, M. Ihara, *J. Am. Chem. Soc.* **1998**, *120*, 4916; b) M. Toyota, T. Waka, M. Ihara, *J. Org. Chem.* **2000**, *65*, 4565; c) M. Toyota, T. Asano, M. Ihara, *Org. Lett.* **2005**, *7*, 3929; d) E. C. Cherney, J. M. Lopchuk, J. C. Green, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 12592; e) A. Abad, C. Agullo, A. C. Cunat, I. A. Marzal, A. Gris, I. Navarro, C. R. Arellanoy, *Tetrahedron* **2007**, *63*, 1664; f) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, Y. Hayase, *J. Am. Chem. Soc.* **1963**, *85*, 2342; g) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, Y. Hayase, *J. Am. Chem. Soc.* **1967**, *89*, 1483; h) S. Masamune, *J. Am. Chem. Soc.* **1964**, *86*, 291; i) R. W. Guthrie, Z. Valenta, K. Wiesner, *Tetrahedron Lett.* **1966**, *7*, 4645; j) M. Ihara, M. Suzuki, K. Fukumoto, T. Kametani, C. Kabuto, *J. Am. Chem. Soc.* **1988**, *110*, 1963; k) M. Ihara, M. Suzuki, K. Fukumoto, T. Kametani, C. Kabuto, *J. Am. Chem. Soc.* **1990**, *112*, 1164; l) X.-Y. Liu, H. Cheng, X.-H. Li, Q.-H. Chen, L. Xu, F.-P. Wang, *Org. Biomol. Chem.* **2012**, *10*, 1411.

[8] a) Z.-G. Liu, L. Xu, Q.-H. Chen, F.-P. Wang, *Tetrahedron* **2012**, *68*, 159; b) H. Cheng, L. Xu, D.-L. Chen, Q.-H. Chen, F.-P. Wang, *Tetrahedron* **2012**, *68*, 1171; c) R.-H. Mei, Z.-G. Liu, H. Cheng, F.-P. Wang, *Org. Lett.* **2013**, *15*, 2206; d) H. Cheng, F.-H. Zeng, D. Ma, M.-L. Jiang, L. Xu, F.-P. Wang, *Org. Lett.* **2014**, *16*, 2299.

[9] For an example of radical-mediated lactone migration from γ-lactone to δ-lactone, see: a) M. Furber, P. Kraft-Klaunzer, L. N. Mander, M. Pour, T. Yamaguchi, N. Murofushi, H. Yamane, H. Schraudolf, *Aust. J. Chem.* **1995**, *48*, 427. For a review of 1,2-acyloxy migration, see: b) A. L. J. Beckwith, D. Crich, P. J. Duggan, Q. Yao, *Chem. Rev.* **1997**, *97*, 3273.

[10] H.-Y. Liu, S. Gao, Y.-T. Di, C.-X. Chen, Y. Lü, L. Zhang, Q.-T. Zheng, X.-J. Hao, *Helv. Chim. Acta* **2007**, *90*, 1386.

[11] a) B. M. Trost, A. C. Gutierrez, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 9206; b) B. M. Trost, E. M. Ferreira, A. C. Gutierrez, *J. Am. Chem. Soc.* **2008**, *130*, 16176; c) B. M. Trost, L. Dong, G. M. Schroeder, *J. Am. Chem. Soc.* **2005**, *127*, 2844; d) B. M. Trost, D. Toste, *J. Am. Chem. Soc.* **2002**, *124*, 5025.

[12] a) Y.-K. Chen, R. K. Peddinti, C.-C. Liao, *Chem. Commun.* **2001**, 1340; b) S. K. Chittimalla, H. Y. Shiao, C. C. Liao, *Org. Biomol. Chem.* **2006**, *4*, 2267.

[13] a) J.-T. Hwang, C.-C. Liao, *Tetrahedron Lett.* **1991**, *32*, 6583; b) G. A. Molander, G. Hahn, *J. Org. Chem.* **1986**, *51*, 1135.

[14] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[15] J. G. McMurry, W. J. Scott, *Tetrahedron Lett.* **1983**, *24*, 979.

[16] J. K. Stille, P. K. Wong, *J. Org. Chem.* **1975**, *40*, 532.
[17] a) J. L. Herrmann, G. R. Kieczykowski, R. H. Schlessinger, *Tetrahedron Lett.* **1973**, *14*, 2433; b) I. Kuwajima, H. Urabe, *Org. Synth.* **1988**, *66*, 87.
[18] Protection of the C15 carbonyl group of **21** as an ethylene ketal group or the C15 hydroxy group as a MOM group all failed the *m*-CPBA epoxidation of the C6-C7 olefin, whereas direct epoxidation of ketone **21** led to several Baeyer–Villiger side reactions without epoxidation of the double bond.
[19] Attempts to subject the corresponding iodolactone of **23** to radical-mediated lactone migration failed, resulting in dehalogenation or decomposition under various conditions.
[20] CCDC 1409825 (**25**) and 1409826 (**31**) contain the supplementary crystallography data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[21] a) J. Hibino, T. Okazoe, K. Takai, H. Nozaki, *Tetrahedron Lett.* **1985**, *26*, 5579; b) K. Takai, T. Kakiuchi, Y. Kataok, K. Utimoto, *J. Org. Chem.* **1994**, *59*, 2668.
[22] H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 569.
[23] B. S. Bal, W. E. Childers Jr, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.
[24] J. H. Han, Y. E. Kwon, J. H. Sohn, D. H. Ryu, *Tetrahedron* **2010**, *66*, 1673.
[25] a) J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330; *Angew. Chem.* **1971**, *83*, 355; b) S. Danishefsky, T. Kitahara, R. McKee, P. F. Schuda, *J. Am. Chem. Soc.* **1976**, *98*, 6715; c) E. J. Corey, A. G. Myers, *J. Am. Chem. Soc.* **1985**, *107*, 5574; d) S. Breitler, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 11168; *Angew. Chem.* **2013**, *125*, 11375.
[26] For selected examples of Mislow–Evans rearrangements, see: a) C. He, C.-L. Zhu, C.-C. Tseng, H.-F. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 13256; *Angew. Chem.* **2013**, *125*, 13498; b) G. Majetich, J. S. Song, C. Ringold, G. A. Nemeth, M. G. Newton, *J. Org. Chem.* **1991**, *56*, 3973; c) D. A. Evans, G. C. Andrews, C. L. Sims, *J. Am. Chem. Soc.* **1971**, *93*, 4956; d) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4869.
[27] The configuration of C19-OH in natural spiraminol (**5**) was not determined. See Ref. [5a].
[28] For selected examples of collective synthesis, see: a) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183; b) H. Li, X. Wang, B. Hong, X. Lei, *J. Org. Chem.* **2013**, *78*, 800; c) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin, Y.-J. Shang, *Chem. Eur. J.* **2013**, *19*, 2539.

Received: September 25, 2015
Published online: November 6, 2015

