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Drug Discovery

Generating Skeletal Diversity from the C_{19}-Diterpenoid Alkaloid Deltaline: A Ring-Distortion Approach

Qi-Feng Chen, Feng-Peng Wang,* and Xiao-Yu Liu*[a]

Abstract: The development of new drugs calls for large collections of diverse molecules with considerable complexity. Ring distortion of natural products provides an efficient and facile approach to access new architectures with intriguing biological activities, by harnessing their inherent complexity. In this study, such a strategy has been explored on an abundant C_{19}-diterpenoid alkaloid, deltaline, enabling the synthesis of 32 new derivatives bearing a broad spectrum of unique scaffolds. Extensive spectroscopic studies including X-ray crystallographic analyses strongly supported the structures of the obtained novel skeletons, which present comparable opportunities with the great contributions made by nature for discovery of new lead compounds.

Introduction

Historically, natural products have long been an inspiration for the development of organic chemical methodologies and theories, promotion of modern spectroscopic technologies, and more importantly, discovery of new drugs for treating diseases.[1] Undoubtedly, natural products keep offering considerable opportunities for finding novel lead structures with therapeutic efficacy in modern drug research.[2] The main reason is that natural products and their derivatives tend to possess architecturally complex three-dimensional skeletons with rich stereogenic centers and sp^3 carbon atoms, allowing specific modulation of the functions of biomacromolecules in living systems. Nevertheless, as the most basic and essential element of drug discovery, how to access such collections of natural-product-like compounds with significant complexity and diversity remains a notable and long-term challenge.

Since the traditional efforts of identification of new natural products from the natural sources are uncertain, several creative strategies have been developed to realize collections of complex molecules. Among them, diversity-oriented synthesis,[3] biology-oriented synthesis,[4] function-oriented synthesis,[5] and synthesis of natural-product-inspired scaffolds/libraries,[6] are established methods that focus on efficient generation of complex and diversified structures from simple starting materials. In contrast, natural products, with inherent structural complexity, have been naturally employed as launch points to provide distinct derivatives.[7] Recently, an elegant ring-distortion approach was initiated by Hergenrother and co-workers, to construct highly diverse collections of complex molecules from readily available natural products (Figure 1).[8] The new concept

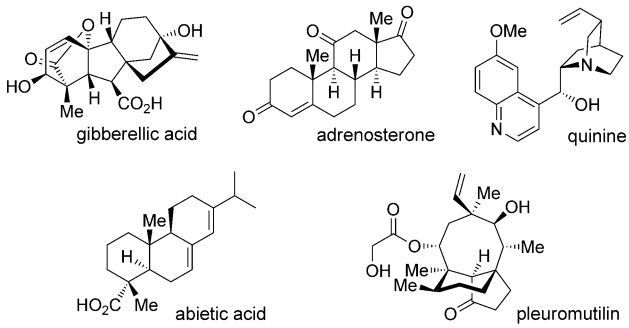

Figure 1. Natural products investigated on the basis of ring-distortion reactions by the Hergenrother group.

has been concentrated on rapid scaffold diversification through ring-distortion reactions (for example, ring cleavage, expansion, fusion, and rearrangement), aiming at achieving complexity-to-diversity, which serves as a superb complement to the existing methods.[9]

Due to the structural intricacy and variety, the polycyclic diterpenes and their corresponding alkaloids have exhibited all-pervasive biological functions and applications, and thus attracted enormous research interests over centuries.[10] As our ongoing pursuit of such fantastic molecules,[10c,11] we disclose herein the synthesis of complex and diverse scaffolds from the C_{19}-diterpenoid alkaloid deltaline (**1**, Figure 2), by utilizing the ring-distortion strategy.

Deltaline (also known as eldeline) was first isolated from *Delphinium occidentale* in 1936,[12] and later found to be widely

[a] *Q.-F. Chen, Prof. Dr. F.-P. Wang, Dr. X.-Y. Liu*
Key Laboratory of Drug Targeting and Drug Delivery
Systems of the Ministry of Education and
Department of Chemistry of Medicinal Natural Products
West China School of Pharmacy
Sichuan University, Chengdu 610041 (P. R. China)
E-mail: wfp@scu.edu.cn
xyliu@scu.edu.cn

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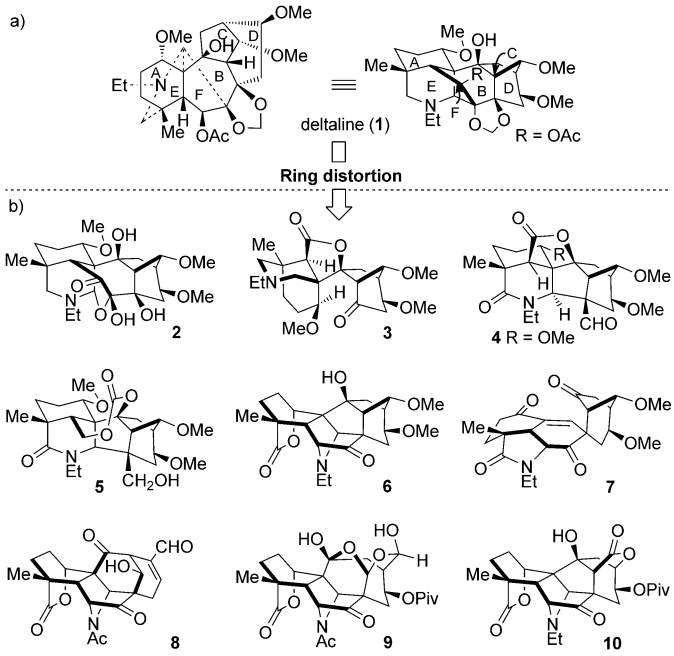
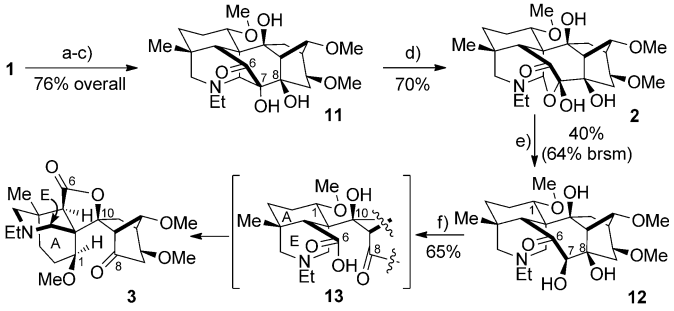


Figure 2. a) Structure of deltaline and b) overview of its skeletal diversification through a ring-distortion strategy.

distributed and as one of the most abundant alkaloids in the plants from the genus *Delphinium*.[13] This compound is distinctive as a nicotinic acetylcholine receptor antagonist,[14] and structurally characterized by its hexacyclic, cage-like framework and densely oxygenated functionalities (one acetate, one hydroxyl, one methylenedioxy, and three methoxy groups). Previous explorations of the chemical reactivity of **1** and its derivatives have been well documented in the literature,[15] whereas only simple transformations were concerned in most cases. Therefore deltaline becomes an attractive platform for complexity-to-diversity studies.

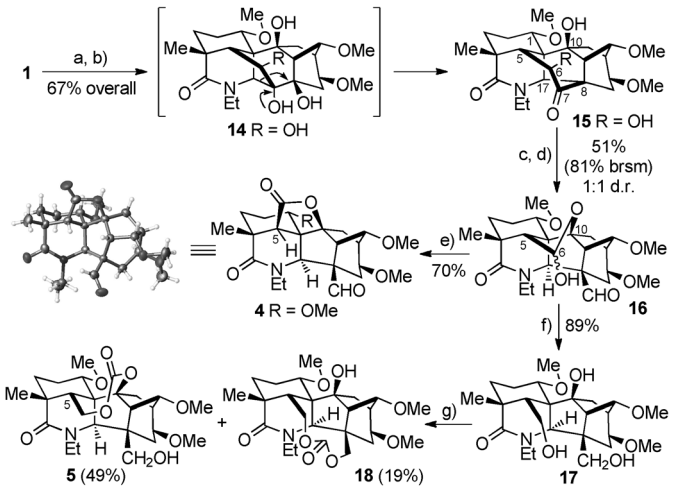
Results and Discussion

To begin with, the highly oxygenated B-ring provides vital synthetic handles for creating diverse molecules. As illustrated in Scheme 1, saponification followed by oxidation of the resulting secondary alcohol delivered the C6 ketone. The corresponding 7,8-diol **11** was then obtained by treatment with 50% H_2SO_4 solution at room temperature.[15o] According to the modified Edwards protocol,[16] exposure of **11** to $Pb(OAc)_4$ resulted in the efficient formation of aminal **2**, representing a ring expansion product of the deltaline core. With its further conversion into the ruptured intermediate **12** by catalytic hydrogenation, a unique pentacyclic spiro-γ-lactone **3** was thus generated in the presence of Jones reagent. The reaction was postulated to occur through acid **13** by a double oxidative cleavage with loss of C7, followed by lactonization from 10-OH to the carboxylic acid at C6. Full interpretation of the 1D and 2D NMR spectroscopic data of **3** confirmed its structure (see the Supporting Information).



Scheme 1. Modifications on B- and F-rings from triol **11**: a) 5% NaOH/MeOH, RT, 1 h; b) Jones reagent, acetone, 0 °C, 0.5 h; c) 50% H_2SO_4, RT, 24 h, 76% (over 3 steps); d) $Pb(OAc)_4$, HOAc, RT, 0.5 h, 70%; e) H_2, PtO_2, HOAc, RT, 12 h, 40% (64% brsm); f) Jones reagent, acetone, 0 °C, 10 min, 65%. brsm = based on recovered starting material.

Besides the oxidative cleavage, the 7,8-vicinal diol was envisaged to be an appropriate substrate to participate in a Pinacol rearrangement event.[15o] In this context, after having the corresponding lactam from $KMnO_4$ oxidation, we were pleased to find that the use of 10% H_2SO_4 solution under reflux realized not only the cleavage of methylenedioxy group (i.e. **14**), but also the desired Pinacol rearrangement product **15** in one pot (Scheme 2). The so-obtained framework itself belongs to one



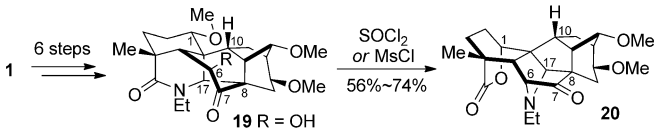
Scheme 2. Pinacol rearrangement of 7,8-diol and further diversification: a) $KMnO_4$, acetone, H_2O, HOAc, RT, 1 h, 90%; b) 10% H_2SO_4, reflux, 5 h, 74%; c) $NaBH_4$, THF, H_2O, RT, 22 h; d) $Pb(OAc)_4$, PhH, 0 °C, 4 h, 51% (81% brsm, over 2 steps), 1:1 d.r.; e) PCC, 4 Å MS, CH_2Cl_2, RT, 14 h, 70%; f) $NaBH_4$, THF, H_2O, RT, 16 h, 89%; g) triphosgene, Py, CH_2Cl_2, −15 °C, 1.5 h, **5** (49%), **18** (19%). MS = molecular sieves, PCC = pyridinium chlorochromate.

type of the naturally occurring C_{19}-diterpenoid alkaloids,[11d] which may help to explain the excellent regioselectivity observed during the rearrangement.

Further skeletal diversity would be achieved by elaborating the newly formed six-membered ring (i.e. the rearranged F ring) in **15**. As a consequence, the 6,7-diol from $NaBH_4$ reduction was directly subjected to $Pb(OAc)_4$, enabling the ring cleavage of **15**, with a concomitant hemiacetal formation be-

tween C6 aldehyde and the free alcohol at C10. Oxidation of the epimeric hemiacetal **16** employing PCC gave rise to the stereochemically pure lactone **4**,[17] the structure of which was unequivocally identified by X-ray crystallographic analysis. Interestingly, epimerization of C5 stereochemistry was observed for compound **4**. Since the β-orientation of H5 in both **16** and its derivative **5** was verified by detailed NOE studies (see the Supporting Information), it was suggested that the epimerization occurred during the PCC oxidation, leading to the thermodynamically more stable product. Additionally, reduction of **16** by $NaBH_4$ afforded triol **17**, which upon treatment with triphosgene produced two unprecedented cyclic carbonates **5** (49%) and **18** (19%).[18]

Our previous studies have shown that,[15o] by introducing a leaving group at C6, an interesting sequence of transformations took place on compound **19** to furnish an unusual heptacyclic core **20**, through the forging of the pivotal N–C6 bond, accompanied by lactone formation, and methyl ether and lactam cleavage (Scheme 3). The key intermediate **19**, prepared

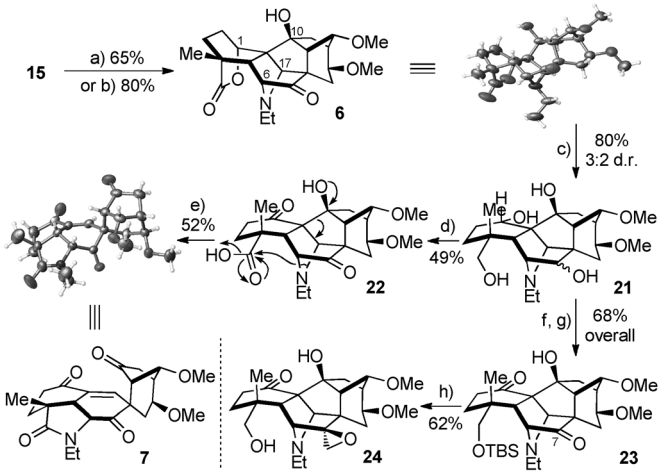


Scheme 3. Our previous synthesis of the heptacyclic compound **20**.

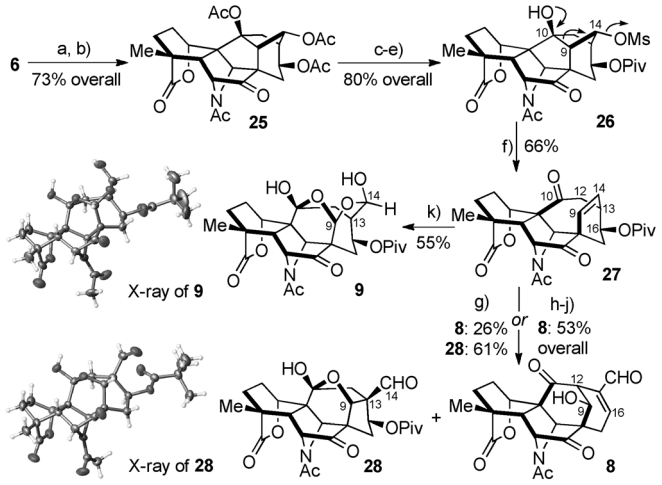
from deltaline (**1**) over six steps, was an analogue of **15**, with the only difference at the C10-position. A similar transformation was envisioned to occur on compound **15**, which was rapidly synthesized in only two steps from **1**. On the other hand, the presence of 10-OH in this series offered more choices for further diversification.

As expected, exposure of **15** to triphosgene or MsCl in the presence of pyridine furnished the heptacyclic system **6** (confirmed by X-ray crystallography) with remarkable efficiency (Scheme 4). Cleavage of the lactone in **6** by reduction with $LiAlH_4$ gave rise to tetraol **21** as a pair of inseparable diastereomers. The latter, after being converted to carboxylic acid **22**, underwent vacuum pyrolysis to generate a novel pentacyclic lactam **7**, the structure of which was unambiguously determined by the X-ray crystallographic data. The reaction was proposed to be initiated by a Grob-fragmentation-like pathway and terminated with a lactam formation.[19] On the other hand, elaboration of tetraol **21** to the spiroepoxide[20] **24** was achieved in three steps: 1) selective silyl protection of the primary alcohol, 2) oxidation of the secondary hydroxyl groups to ketones, and 3) epoxide formation at C7 carbonyl group through the Corey–Chaykovsky protocol.[21] Note that the desilylation occurred slowly under the reaction conditions and reached completion with prolonged time. In addition, the selective manner in the production of spiroepoxide **24** was also impressive, which was speculated to be dependent on the steric effect of the substrate.

As a versatile intermediate, compound **6** offered further entries to novel derivatives with conceivable complexity and



Scheme 4. Synthesis of **6** and diversification of its lactone cleavage derivatives: a) triphosgene, Py, CH_2Cl_2, RT, 12 h, 65%; b) MsCl, Py, 50 °C, 5 h, 80%; c) $LiAlH_4$, THF, 50 °C, 24 h, 80%, 3:2 d.r.; d) Jones reagent, acetone, 40 °C, 24 h, 49%; e) 15 mmHg, 180 °C, 15 min, 52%; f) TBSCl, imidazole, DMF, RT, 2 h, 79%; g) DMP, $NaHCO_3$, CH_2Cl_2, RT, 2 h, 86%; h) $Me_3OS^+I^-$, NaH, DMSO, THF, 60 °C, 24 h, 62%. DMP = Dess–Martin periodinane, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

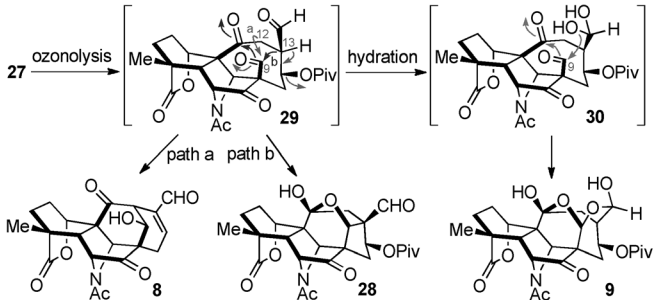


Scheme 5. Synthesis of diverse skeletons **8**, **9**, **27**, and **28** from **6**: a) NBS, HOAc, RT, 1 h, 93%; b) 6.5% HBr/HOAc, 85 °C, 50 h, 79%; c) 5% NaOH/MeOH, RT, 3 h; d) PivCl, DMAP, Py. RT, 3 h; e) MsCl, Py., RT, 2 h, 80% (over 3 steps); f) NaH, CH_2Cl_2, RT, 6 h, 66%; g) O_3, CH_2Cl_2, −78 °C, 10 min; then Me_2S, Et_3N, RT, 3.5 h, **28** (61%), **8** (26%); h) 0.25% NaOH/MeOH, RT, 5 h; i) MsCl, Py, RT, 2 h, 89% (over 2 steps); j) O_3, CH_2Cl_2, −78 °C, 10 min; then Me_2S, Et_3N, RT, 2 h, **8** (60%); k) O_3, CH_2Cl_2, −78 °C, 10 min; then Me_2S, *p*TsOH, RT, 3 h, 55%. DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, Piv = pivaloyl, *p*TsOH = *para*-toluenesulfonic acid.

diversity, through distortions of the C/D rings. Specifically, manipulations of *N*-ethyl and methoxy groups led to the anticipated acetates **25** (Scheme 5).[15k,22] A three-step procedure was then applied to secure the important precursor **26**, with an 80% overall yield. At this stage, an impressive Grob fragmentation proceeded smoothly in the presence of sodium hydride at room temperature, giving access to the ring cleavage product **27**. It is noteworthy that the olefinic ketone **27**

became particularly attractive due to its latent reactivity towards ozonolysis and subsequent transformations.

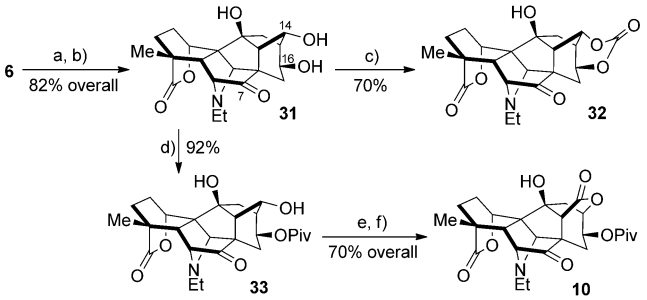
Accordingly, subjecting **27** to ozone followed by quenching the reaction with Me_2S and Et_3N (Scheme 5) gave two separable products, **8** (26%) and **28** (61%). Intramolecular aldol addition of the resultant dialdehyde from ozonolysis accounted for the generation of both products,[23] the structures of which were established by extensive spectroscopic analyses, including X-ray crystallography of **28**. As shown in Scheme 6, construction of the C9–C12 bond along with the elimination of a pivalic acid afforded **8** (Scheme 6, path a), whereas the assembly of the C9–C13 bond with ensuing hemiacetal formation allowed for the production of **28** (Scheme 6, path b). Without adding bases (such as Et_3N) into the reaction mixture was insignificant to alter the ratio between compounds **8** and **28**. To improve the yield of **8**, a mesylate was installed at C16 to replace the pivalate, serving as a better leaving group. As a result, the facile formation of enal moiety prevented the addition from C13 to C9, thereby producing hexacyclic **8** exclusively.



Scheme 6. Possible pathways for the formation of **8**, **9**, and **28**.

Furthermore, the possible impact of acidic additive on the profile of products was investigated (Scheme 5). As expected, addition of *p*TsOH into the reaction mixture gave an entirely different spot, which was identified as the heptacycle **9** and confirmed by an X-ray crystallographic study. The key to the formation of a characteristic 1,3-dioxepane-4,7-diol unit in **9** relied on a consecutive acetalization process from the dialdehyde **29** after hydration (Scheme 6).

Without bothering the *N*-ethyl group, direct O-demethylation followed by saponification of compound **6** furnished triol **31** (Scheme 7). Treating the latter with triphosgene yielded a ring-fusion product **32**. In addition, we envisioned that a ring expansion version might be generated by a Baeyer–Villiger oxidation of the C7 ketone. Despite numerous efforts, the carbonyl group at C7 was revealed to be inert to the oxidation conditions, probably due to its spatially crowded environment in the rigidly heptacyclic nucleus. In contrast, the C14 ketone displayed positive reactivity towards related oxidants. Therefore, selective protection of the sterically less hindered hydroxyl group at C16 in the intermediate **31** was achieved, similar to that described in Scheme 5. After Jones oxidation of C14 alcohol, the expected Baeyer–Villiger reaction took place smoothly



Scheme 7. Generating diversity from intermediate **31**: a) 6.5% HBr/HOAc, 85 °C, 65 h, 84%; b) 5% NaOH/MeOH, RT, 4 h, 98%; c) triphosgene, Py., CH_2Cl_2, RT, 15 h, 70%; d) PivCl, DMAP, Py, RT, 3 h, 92%; e) Jones reagent, acetone, 0 °C, 10 min, 98%; f) H_2O_2/HCO_2H (1:1), RT, 2.5 h, 71%.

to deliver the lactone **10**,[17] promoted by a mixture of H_2O_2 and HCO_2H.[24] The location of the newly established lactone was assigned on the basis of $^1H,^1H$-COSY and HMBC experiments.

Conclusions

In summary, we have described an expedient access to highly complex and diverse scaffolds from the naturally occurring C_{19}-diterpenoid alkaloid deltaline, by means of a ring-distortion strategy. The endeavors of distorting different rings have generated not only the skeletal diversity, but also an array of widespread structural moieties embedded in these carbon frameworks, which further demonstrates the versatility of the promising protocol. All the 32 products described in this study are new compounds, prepared within ten synthetic steps and on 12–9200 mg scales (see the Supporting Information), thus providing entries to identify potentially new chemotypes. Moreover, it is particularly remarkable that, utility of simple chemical methods and reagents enables efficient and facile transformations in complex molecular settings. Most importantly, creation of novel skeletons and their derivatives in this study sets the stage for an in-depth exploration of the biological and medicinal applications.

Experimental Section

All the experimental details are presented in the Supporting Information.

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Keywords: alkaloids · deltaline · drug discovery · natural products · X-ray crystallography

[1] D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*, 303 – 336.
[2] a) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311 – 335; b) G. M. Cragg, D. J. Newman, *Biochim. Biophys. Acta* **2013**, *1830*, 3670 – 3695; c) M. S. Butler, A. A. B. Robertson, M. A. Cooper, *Nat. Prod. Rep.* **2014**, *31*, 1612 – 1661.
[3] a) S. L. Schreiber, *Science* **2000**, *287*, 1964 – 1969; b) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46 – 58; *Angew. Chem.* **2004**, *116*, 48 – 60; c) D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74 – 84; d) W. R. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80; e) C. J. O'Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444 – 4456.
[4] a) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10800 – 10826; *Angew. Chem.* **2011**, *123*, 10990 – 11018; b) H. Lachance, S. Wetzel, K. Kumar, H. Waldmann, *J. Med. Chem.* **2012**, *55*, 5989 – 6001.
[5] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40 – 49.
[6] a) H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen, M. D. Shair, *J. Am. Chem. Soc.* **2001**, *123*, 6740 – 6741; b) B. C. Goess, R. N. Hannoush, L. K. Chan, T. Kirchhausen, M. D. Shair, *J. Am. Chem. Soc.* **2006**, *128*, 5391 – 5403; c) K. J. Frankowski, V. Setola, J. M. Evans, B. Neuenswander, B. L. Roth, J. Aubé, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6727 – 6732; d) H. Oguri, T. Hiruma, Y. Yamagishi, H. Oikawa, A. Ishiyama, K. Otoguro, H. Yamada, S. Omura, *J. Am. Chem. Soc.* **2011**, *133*, 7096 – 7105; e) H. Mizoguchi, H. Oikawa, H. Oguri, *Nat. Chem.* **2014**, *6*, 57 – 64; f) M. C. McLeod, G. Singh, J. N. Plampin III, D. Rane, J. L. Wang, V. W. Day, J. Aubé, *Nat. Chem.* **2014**, *6*, 133 – 140; g) J. Zhang, J. Wu, B. Hong, W. Ai, X. Wang, H. Li, X. Lei, *Nat. Commun.* **2014**, *5*, 4614.
[7] For recent reviews, see: a) K. C. Morrison, P. J. Hergenrother, *Nat. Prod. Rep.* **2014**, *31*, 6 – 14; b) O. Robles, D. Romo, *Nat. Prod. Rep.* **2014**, *31*, 318 – 334; c) J. Szychowski, J.-F. Truchon, Y. L. Bennani, *J. Med. Chem.* **2014**, *57*, 9292 – 9308; for recent examples, see: d) B. R. Balthaser, M. C. Maloney, A. B. Beeler, J. A. Porco Jr., J. K. Snyder, *Nat. Chem.* **2011**, *3*, 969 – 973; e) J. Li, J. S. Cisar, C.-Y. Zhou, B. Vera, H. Williams, A. D. Rodríguez, B. F. Cravatt, D. Romo, *Nat. Chem.* **2013**, *5*, 510 – 517; f) O. E. Hutt, T. L. Doan, G. I. Georg, *Org. Lett.* **2013**, *15*, 1602 – 1605; g) C. Ding, Y. Zhang, H. Chen, C. Wild, T. Wang, M. A. White, Q. Shen, J. Zhou, *Org. Lett.* **2013**, *15*, 3718 – 3721; h) A. J. Grenning, J. K. Snyder, J. A. Porco Jr., *Org. Lett.* **2014**, *16*, 792 – 795; i) Q. Michaudel, G. Journot, A. Regueiro-Ren, A. Goswami, Z. Guo, T. P. Tully, L. Zou, R. O. Ramabhadran, K. N. Houk, P. S. Baran, *Angew. Chem. Int. Ed.* **2014**, *53*, 12091 – 12096; *Angew. Chem.* **2014**, *126*, 12287 – 12292.
[8] a) R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood, M. F. Richter, P. J. Hergenrother, *Nat. Chem.* **2013**, *5*, 195 – 202; b) R. J. Rafferty, R. W. Hicklin, K. A. Maloof, P. J. Hergenrother, *Angew. Chem. Int. Ed.* **2014**, *53*, 220 – 224; *Angew. Chem.* **2014**, *126*, 224 – 228; c) R. W. Hicklin, T. L. López Silva, P. J. Hergenrother, *Angew. Chem. Int. Ed.* **2014**, *53*, 9880 – 9883; *Angew. Chem.* **2014**, *126*, 10038 – 10041.
[9] J.-P. Krieger, G. Ricci, D. Lesuisse, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2014**, *53*, 8705 – 8708; *Angew. Chem.* **2014**, *126*, 8849 – 8852.
[10] For selected reviews, see: a) L. N. Mander, *Nat. Prod. Rep.* **2003**, *20*, 49 – 69; b) H.-D. Sun, S.-X. Huang, Q.-B. Han, *Nat. Prod. Rep.* **2006**, *23*, 673 – 698; c) F.-P. Wang, Q.-H. Chen, X.-Y. Liu, *Nat. Prod. Rep.* **2010**, *27*, 529 – 570; d) E. C. Cherney, P. S. Baran, *Isr. J. Chem.* **2011**, *51*, 391 – 405; e) Z.-L. Zhou, Y.-X. Yang, J. Ding, Y.-C. Li, Z.-H. Miao, *Nat. Prod. Rep.* **2012**, *29*, 457 – 475; f) K. Wada in *Studies in Natural Products Chemistry, Vol. 38* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **2012**, pp. 191 – 223; g) J. R. Hanson, *Nat. Prod. Rep.* **2015**, *32*, 76 – 87.
[11] For reviews, see: a) F.-P. Wang, X.-T. Liang in *The Alkaloids: Chemistry and Physiology, Vol. 42* (Ed.: G. A. Cordell), Academic, San Diego, **1992**, pp. 151 – 247; b) F.-P. Wang, X.-T. Liang in *The Alkaloids: Chemistry and Biology, Vol. 59* (Ed.: G. A. Cordell), Elsevier, New York, **2002**, pp. 1 – 280; c) F.-P. Wang, Q.-H. Chen, X.-T. Liang in *The Alkaloids: Chemistry and Biology, Vol. 67* (Ed.: G. A. Cordell), Elsevier, New York, **2009**, pp. 1 – 78; d) F.-P. Wang, Q.-H. Chen in *The Alkaloids: Chemistry and Biology, Vol. 69* (Ed.: G. A. Cordell), Elsevier, New York, **2010**, pp. 1 – 577.
[12] J. F. Couch, *J. Am. Chem. Soc.* **1936**, *58*, 684 – 685.
[13] For selected reports, see: a) S. W. Pelletier, N. V. Mody, O. D. Dailey Jr., *Can. J. Chem.* **1980**, *58*, 1875 – 1879; b) S. W. Pelletier, O. D. Dailey Jr., N. V. Mody, J. D. Olsen, *J. Org. Chem.* **1981**, *46*, 3284 – 3293; c) Q. P. Jiang, W. L. Sung, *Heterocycles* **1985**, *23*, 11 – 15; d) S. W. Pelletier, S. A. Ross, P. Kulanthaivel, *Tetrahedron* **1989**, *45*, 1887 – 1892; e) C. Y. Zhang, W. L. Sung, D. H. Chen, *Fitoterapia* **1993**, *64*, 188 – 189; f) F.-Z. Chen, D.-L. Chen, Q.-H. Chen, F.-P. Wang, *J. Nat. Prod.* **2009**, *72*, 18 – 23.
[14] a) P. Dobelis, J. E. Madl, J. A. Pfister, G. D. Manners, J. P. Walrond, *J. Pharmacol. Exp. Ther.* **1999**, *291*, 538 – 546; b) K. D. Welch, J. A. Pfister, F. G. Lima, B. T. Green, D. R. Gardner, *Toxicol. Appl. Pharmacol.* **2013**, *266*, 366 – 374.
[15] a) M. Carmack, J. P. Ferris, J. Harvey, P. T. Magat, E. W. Martin, D. W. Mayo, *J. Am. Chem. Soc.* **1958**, *80*, 497; b) P. Kulanthaivel, S. W. Pelletier, *Tetrahedron Lett.* **1987**, *28*, 3883 – 3886; c) P. Kulanthaivel, S. W. Pelletier, *Tetrahedron* **1988**, *44*, 4313 – 4320; d) A. S. Narzullaev, M. S. Yunusov, A. M. Moisenkov, S. S. Sabirov, *Khim. Prir. Soedin.* **1989**, 372 – 375; e) H. K. Desai, H. P. Chokshi, S. W. Pelletier, *J. Nat. Prod.* **1989**, *52*, 1296 – 1302; f) X. Liang, H. K. Desai, B. S. Joshi, S. W. Pelletier, *Heterocycles* **1990**, *31*, 1889 – 1894; g) S. K. Srivastava, B. S. Joshi, M. G. Newton, D. Lee, S. W. Pelletier, *Tetrahedron Lett.* **1995**, *36*, 519 – 522; h) Y. Bai, H. K. Desai, S. W. Pelletier, *J. Nat. Prod.* **1995**, *58*, 929 – 933; i) Y.-M. He, C.-L. Zou, Q.-H. Chen, F.-P. Wang, *J. Asian Nat. Prod. Res.* **2007**, *9*, 713 – 720; j) C.-L. Zou, X.-Y. Liu, F.-P. Wang, Q.-H. Chen, *Chem. Pharm. Bull.* **2008**, *56*, 250 – 253; k) C.-L. Zou, H. Ji, G.-B. Xie, D.-L. Chen, F.-P. Wang, *J. Asian Nat. Prod. Res.* **2008**, *10*, 1063 – 1067; l) C.-L. Zou, L. Cai, H. Ji, G.-B. Xie, F.-P. Wang, X.-X. Jian, L. Song, X.-Y. Liu, D.-L. Chen, Q.-H. Chen, *Tetrahedron* **2008**, *64*, 7594 – 7604; m) L. Wang, Q.-H. Chen, F.-P. Wang, *Nat. Prod. Commun.* **2012**, *7*, 721 – 724; n) L. Wang, Q.-F. Chen, F.-P. Wang, *Nat. Prod. Commun.* **2012**, *7*, 1583 – 1586; o) P. Tang, L. Wang, Q.-F. Chen, Q.-H. Chen, X.-X. Jian, F.-P. Wang, *Tetrahedron* **2012**, *68*, 5031 – 5036; p) P. Tang, Q.-F. Chen, L. Wang, Q.-H. Chen, X.-X. Jian, F.-P. Wang, *Tetrahedron* **2012**, *68*, 5668 – 5676; q) P. Tang, L. Wang, Q.-F. Chen, Q.-H. Chen, X.-X. Jian, F.-P. Wang, *Tetrahedron* **2012**, *68*, 6249 – 6256.
[16] O. E. Edwards, M. Los, L. Marion, *Can. J. Chem.* **1959**, *37*, 1996 – 2006.
[17] L. Silva, A. C. Gomes, J. M. L. Rodilla, *Nat. Prod. Commun.* **2011**, *6*, 497 – 504.
[18] H. Zhang, H.-B. Liu, J.-M. Yue, *Chem. Rev.* **2014**, *114*, 883 – 898.
[19] For a related Grob fragmentation via vacuum pyrolysis, see: L. Wang, Q.-F. Chen, F.-P. Wang, *Nat. Prod. Commun.* **2013**, *8*, 1701 – 1704.
[20] a) S. Mo, A. Krunic, B. D. Santarsiero, S. G. Franzblau, J. Orjala, *Phytochemistry* **2010**, *71*, 2116 – 2123; b) C. Li, M. Jiang, M.-P. La, T.-J. Li, H. Tang, P. Sun, B.-S. Liu, Y.-H. Yi, Z. Liu, W. Zhang, *Mar. Drugs* **2013**, *11*, 1565 – 1582.
[21] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353 – 1364.
[22] F.-P. Wang, L. Xu, *Tetrahedron* **2005**, *61*, 2149 – 2167.
[23] For a similar transformation on a different scaffold, see ref. [14].
[24] M. Zhu, X.-Y. Liu, Q.-H. Chen, F.-P. Wang, *J. Asian Nat. Prod. Res.* **2012**, *14*, 441 – 449.

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FULL PAPER

Drug Discovery

Q.-F. Chen, F.-P. Wang, X.-Y. Liu**

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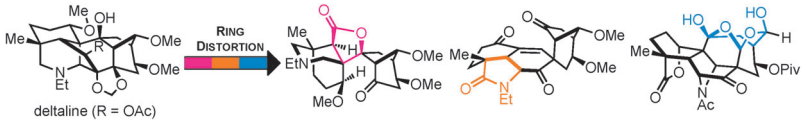
Generating Skeletal Diversity from the C_{19}-Diterpenoid Alkaloid Deltaline: A Ring-Distortion Approach



A ring-distortion strategy has been applied to the synthesis of 32 distinct molecules with significant complexity and diversity, from the C_{19}-diterpenoid alkaloid deltaline (see scheme). Extensive spectroscopic studies strongly supported the structures of the obtained novel skeletons, which present comparable opportunities with the great contributions made by nature for the discovery of new lead compounds.