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Collective Domino Approach toward the Core of Molecules Isolated from the Genus *Schisandra*

Alexandra Bartoli, Gaëlle Chouraqui,* and Jean-Luc Parrain*

Institut des Sciences Moléculaires de Marseille, Aix-Marseille Université, iSm2-UMR CNRS 6263, Campus Saint Jérôme, Service 532, 13397 Marseille Cedex 20, France

gaelle.chouraqui@univ-cezanne.fr; jl.parrain@univ-cezanne.fr

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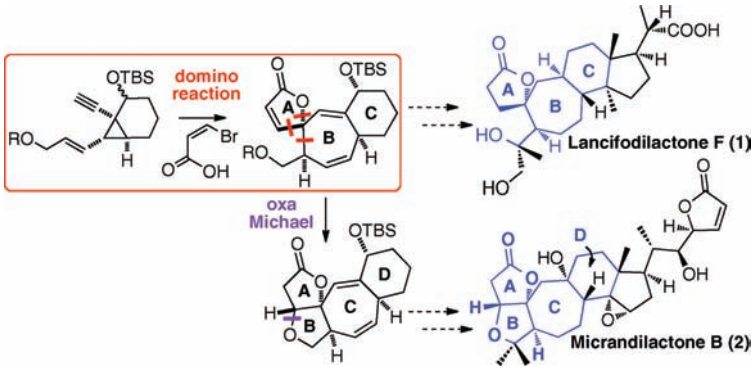
ABSTRACT



A concise route to the ABC and ABCD core of molecules isolated from the genus *Schisandra* has been accomplished. The synthesis demonstrated high atom efficiency employing a new one-pot cascade which sequentially built three rings and a quaternary spirocenter.

Plants of the genus *Schisandra*, belonging to the unique family Schisandraceae, have been used as folk medicines in China for many years. Due to their interesting medicinal properties, these plants have been the subject of extensive investigation in recent years, which has led to the isolation of several novel nortriterpenoids in recent years.[1] Most notably, these highly oxygenated secondary metabolites have been reported to exert anti-HIV activity[1a,2] along with minimal cytotoxicity.[3]

Currently, synthetic organic chemists are able to access any desired complex natural product. The challenge now is to develop more efficient, shorter, and less time-consuming approaches. Collective synthesis, a concept recently introduced by McMillan, mimics nature by using cascade-type reactions and by targeting a common intermediate to access several natural products at once.[4] This philosophy is consistent with the chemistry developed in our laboratory as our main concern is to generate step-, atom-, and time-economical strategies.[5]

(1) For reviews on family Schisandraceae, see (and references therein): (a) Xiao, W.-L.; Li, R.-T.; Huang, S.-X.; Pu, J.-X.; Sun, H.-D. *Nat. Prod. Rep.* **2008**, *25*, 871–891. (b) Whiting, D. A. *Nat. Prod. Rep.* **1990**, *7*, 349–364. (c) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96.

(2) (a) Chen, D. F.; Zhang, S. X.; Wang, H. K.; Zhang, S. Y.; Sun, Q. Z.; Cosentino, M.; Lee, K. H. *J. Nat. Prod.* **1999**, *62*, 94–97. (b) Sun, H. D.; Qiu, S. X.; Lin, L. Z.; Wang, Z. Y.; Lin, Z. W.; Pengsuparp, T.; Pezzuto, J. M.; Fong, H. H. S.; Cordell, C. A.; Farnsworth, N. R. *J. Nat. Prod.* **1996**, *59*, 525–527. (c) Li, R.-T.; Han, Q.-B.; Zheng, Y.-T.; Wang, R.-R.; Yang, L.-M.; Lu, Y.; Sang, S.-Q.; Zheng, Q.-T.; Zhao, Q.-S.; Sun, H.-D. *Chem. Commun.* **2005**, 2936–2938. (d) Xiao, W.-L.; Yang, L.-M.; Gong, N.-B.; Wu, L.; Wang, R.-R.; Pu, J.-X.; Li, X.-L.; Huang, S.-X.; Zheng, Y.-T.; Li, R.-T.; Lu, Y.; Zheng, Q.-T.; Sun, H.-D. *Org. Lett.* **2006**, *8*, 991–994.

(3) (a) Xiao, W.-L.; Lei, C.; Ren, J.; Liao, T.-G.; Pu, J.-X.; Pittman, C. U., Jr.; Lu, Y.; Zheng, Y.-T.; Zhu, H.-J.; Sun, H.-D. *Chem.—Eur. J.* **2008**, *14*, 11584–11592. (b) Xiao, W.-L.; Gong, Y.-Q.; Wang, R.-R.; Weng, Z.-Y.; Luo, X.; Li, X.-N.; Yang, G.-Y.; He, F.; Pu, J.-X.; Yang, L.-M.; Zheng, Y.-T.; Lu, Y.; Sun, H.-D. *J. Nat. Prod.* **2009**, *72*, 1678–1681.

(4) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188.

(5) (a) Coquerel, Y.; Boddaert, T.; Presset, M.; Mailhol, D.; Rodriguez, J. *Ideas in Chemistry and Molecular Sciences*, Advances in Synthetic Chemistry; Pignataro, B., Ed.; Wiley-VCH: Weinheim, Germany, 2010; Vol. 1, Chapter 9, pp 187–202. (b) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085–1109. (c) Lamandé-Langle, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Chem. Commun.* **2010**, 5157–5159.

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The spiro [6.4] ring system contained in a (5,7,6) polycyclic scaffold is a recurring structural motif in numerous natural products of the Schisandraceae family (**1**–**5**)[2c,6] (Figure 1).

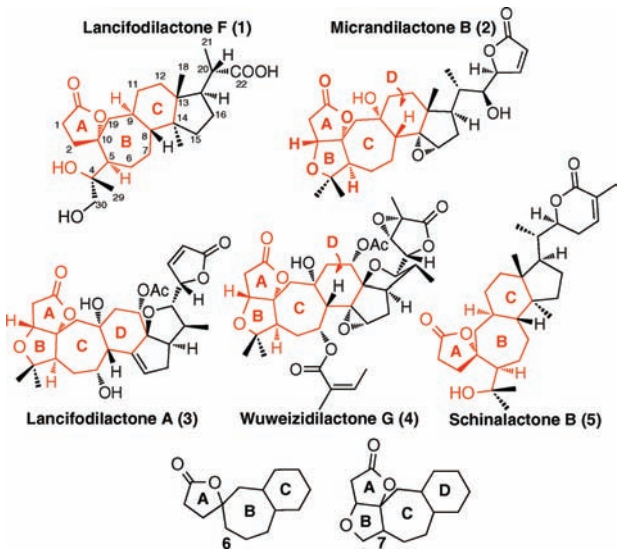


Figure 1. Structure of nortriterpenoids from the family Schisandraceae (**1**–**5**).

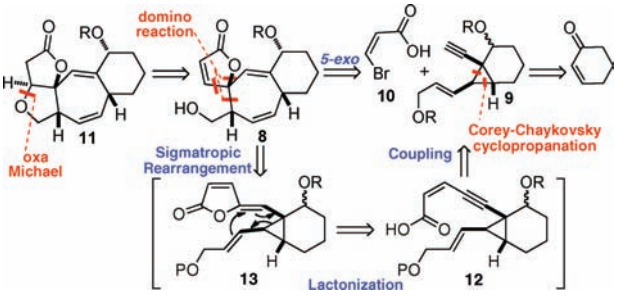
In connection with our continued interest in the construction of spirolactones with concomitant formation of the fused quaternary stereocenter and its application to the synthesis of natural products,[7] we recently embarked upon a program targeting the polycyclic substructures **6** and **7** relevant to these natural products (Figure 1).

In addition to their interesting biological activities, such natural products represent a synthetic challenge for organic chemists. Accordingly, these polycyclic structures feature at least nine stereogenic centers including several quaternary ones (still one of the most difficult tasks in organic synthesis). Studies directed toward the synthesis of nortriterpenoids from the Schisandraceae family have been conducted in several laboratories, but despite the intensity of their efforts,[8] only one total synthesis has been reported to date.[9]

A few years after the isolation of lancifodilactone F,[6a] we envisioned a new flexible domino reaction, which could set the relative stereochemistry of stereocenters C-5, C-8, and C-10 and reach the ABC core of this natural product. Surprisingly, this target seemed to be the only one in the family of related compounds to possess a *cis* relationship between hydrogens H_5 and H_8. Accordingly, it was assigned by Sun et al. through X-ray crystal structure determination so our program was started with confidence. Unfortunately, it subsequently transpired that the X-ray analysis had been incorrectly "transcribed".[1a]

Herein we describe a rapid access to the [6.4] spiro moiety contained in initially assigned substructure **6** and the tetracyclic skeleton **7**.

Scheme 1. Retrosynthetic Analysis



Our retrosynthetic analysis (Scheme 1) of the tricyclic core of molecules isolated from the *Schisandra* genus **8** relies on a one-pot domino reaction to form concomitantly the spiro stereocenter and the [6.4] spirolactone, such that major fragment **9** and acid **10** serve as key building blocks in this project. This analysis reveals the advanced α,β-unsaturated lactone **8**, which could undergo a hetero-Michael addition to complete the other target molecule **11**. Precursor **9**, on the other hand, could be obtained from commercially available cyclohex-2-enone via a Corey–Chaykovsky cyclopropanation.

As outlined in Scheme 1, our strategy involves the development of a cascade in which three individual steps are combined in a synthetic sequence. First a Pd-mediated Sonogashira ene-yne coupling between moieties **9** and **10** would provide the corresponding ynenoic acid **12**. This intermediate could be further transformed into the γ-alkylidene butenolide **13** by the catalysis of Pd(II) via a 5-*exo*-*dig* mechanism.[10] Finally, the *cis* relationship

(6) (a) Xiao, W.-L.; Li, R.-T.; Li, S.-H.; Li, X.-L.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q.-T. *Org. Lett.* **2005**, *7*, 1263–1266. (b) He, F.; Pu, J.-X.; Huang, S.-X.; Wang, Y.-Y.; Xiao, W.-L.; Li, L.-M.; Liu, J.-P.; Zhang, H.-B.; Li, Y.; Sun, H.-D. *Org. Lett.* **2010**, *12*, 1208–1211. (c) Xiao, W.-L.; Yang, S.-Y.; Yang, L.-M.; Yang, G.-Y.; Wang, R.-R.; Zhang, H.-B.; Zhao, W.; Pu, J.-X.; Lu, Y.; Zheng, Y.-T.; Sun, H.-D. *J. Nat. Prod.* **2010**, *73*, 221–225and references therein.

(7) (a) Bartoli, A.; Rodier, F.; Chouraqui, G.; Commeiras, L.; Parrain, J.-L. *Nat. Prod. Rep.* **2011**, *28*, 763–782. (b) Blanc, R.; Héran, V.; Rahmani, R.; Commeiras, L.; Parrain, J.-L. *Org. Biomol. Chem.* **2010**, *8*, 5490–5494.

(8) (a) Maity, S.; Matcha, K.; Ghosh, S. *J. Org. Chem.* **2010**, *75*, 4162–4200. (b) Mehta, G.; Bhat, B. A. *Tetrahedron Lett.* **2009**, *50*, 2474–2477. (c) Mehta, G.; Bhat, B. A.; Kumara, T. H. S. *Tetrahedron Lett.* **2009**, *50*, 6597–6600. (d) Cordonnier, M.-C. A.; Kan, S. B. J.; Anderson, E. A. *Chem. Commun.* **2008**, 5818–5820. (e) Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 2111–2113. 2115–2118, and 3781–3784. (f) Qiaoling, W.; Chen, C. *Org. Lett.* **2008**, *10*, 1223–1226. (g) Zhang, Y. D.; Ren, W. W.; Lan, Y.; Xiao, Q.; Wang, K.; Xu, J.; Chen, J. H.; Yang, Z. *Org. Lett.* **2008**, *10*, 665–668. (h) Fischer, D.; Theodorakis, E. A. *Eur. J. Org. Chem.* **2007**, 4193–4196. (i) Zhang, Y.-D.; Tang, Y.-F.; Luo, T.-P.; Shen, J.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2006**, *8*, 107–110. (j) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 885–888.

(9) Xiao, Q.; Ren, W.-W.; Chen, Z.-X.; Sun, T.-W.; Li, Y.; Ye, Q.-D.; Gong, J.-X.; Meng, F.-K.; You, L.; Liu, Y.-F.; Zhao, M.-Z.; Xu, L.-M.; Shan, Z.-H.; Shi, Y.; Tang, Y.-F.; Chen, J.-H; Yang, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 7373–7377.

(10) (a) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1993**, *34*, 5963–5966. (b) Kotora, M.; Negishi, E.-i. *Synthesis* **1997**, 121–128.

(11) For divinylcyclopropane-cycloheptadiene rearrangement, see: (a) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1–133. (b) Wong, H. N. C.; Hon, M. Y; Tse, C. W; Yip, Y. C *Chem. Rev.* **1989**, *89*, 165–168 and references therein.

between the alkene substituents onto cyclopropane **13** is conducive to a Cope rearrangement which would lead to cycloheptadiene **8**.[11]

The success of the scheme depends on the stereoselectivity of the Corey–Chaykovsky cyclopropanation that should favor the formation of *cis*-1-ethynyl-2-vinylcyclopropanes in the reaction with 2-substituted cyclohex-2-enone. Encouraged by Wender's results in a similar reaction,[12] the condensation of enone **14**[13] was performed with sulfur ylid **15** (Scheme 2). The three-membered ring **16** was obtained in a quantitative manner and as a single diastereomer. However, the ^{1}H NMR spectral analysis did not allow us to confirm the relative configuration of molecule **17** ($^3J_{Ha-Hb}$ = 6.3 Hz).[14] A further chemoselective reduction of the ketone led to a mixture of two diastereomeric alcohols **17a** and **17b** in a 1:1 ratio and 92% yield.

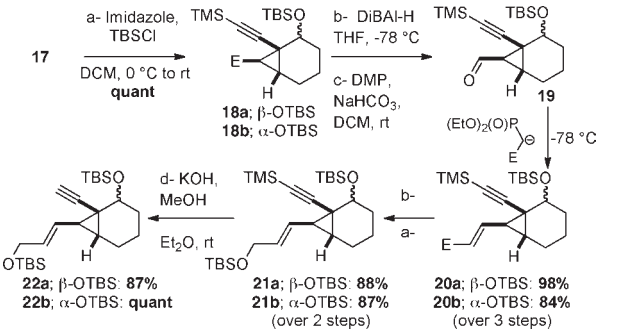
Scheme 2. Preparation of Alcohol **17**

Fortunately, diastereomeric alcohol **17a** proved to be crystalline, and its relative stereochemistry was unambiguously secured through X-ray crystallographic analysis.[15]

Subsequently, both diastereomers **17a** and **17b** were advanced through the same sequence of reactions separately (Scheme 3). The secondary alcohol **17** was quantitatively protected as TBS ether **18**. Subsequent reduction of the ester followed by oxidation with Dess-Martin periodinane provided aldehyde **19** ready for a Horner–Wadsworth–Emmons olefination. This reaction led exclusively to the (*E*)-alkenes **20a** and **20b** in 98 and 84% yield, respectively, over three steps. Reduction of the ester in the presence of DiBAl-H followed by a TBS protection afforded precursors **21a** and **21b** in 87 and 88% yield, respectively, over two steps. Finally, deprotection of alkyne **21** with potassium hydroxide in methanol gave alkyne diastereomers **22** in readiness for the domino key reaction.

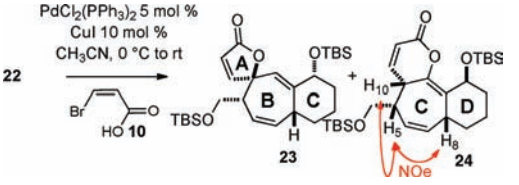
Having in hand precursors **22**, a classical palladium-mediated Sonogashira reaction was first envisaged. When alkyne **22a** was combined with bromoacid **10**, 5 mol % of palladium(II), and 10 mol % of copper(I) iodide in triethylamine and acetonitrile, the expected adduct **23** was not observed, but 10% of tricyclic structure **24** was instead

Scheme 3. Synthesis of Precursors **22**



isolated as a single diastereomer (Table 1, entry 1). This polycyclic scaffold resulted from a 6-*endo-dig* pathway of the lactonization step was the 5-*exo-dig* one. The desired domino reaction product **23** was obtained as a single diastereomer, as well. On the other hand, when diastereomer **22b** was submitted to the same conditions, the path followed in 23% yield (Table 1, entry 2). Of course, the yields of both domino reactions had to be improved, but such a result validated the sequence during which a ring expansion is accompanied by the creation of three single bonds and two stereogenic centers.

Table 1. Conditions of the New Domino Reaction/NOE Experiments



entry	alkyne	additive	yield	yield per step
1	**22a**		10% **24**	46%
2	**22b**		23% **23**	61%
3	**22b**	$2PPh_3$	31% **23**	68%
4	**22a**	$2PPh_3$	16% **24**	54%

Attempts to change the palladium source of the initial Sonogashira coupling reaction, the nature, and the amount of base or the amount and nature of halide (*Z*)-3-iodoacrylic acid did not lead to any yield improvement of the expected adduct **23** and/or **24**. The palladium-free Sonogashira reaction recently developed in the laboratory was also tested, however, without success or improvement.[16]

Ultimately, adding 2 equivs of triphenylphosphine (10 mol %) relative to the palladium catalyst proved to be beneficial as 16 and 31% of adducts **23** and **24** were, respectively, isolated (Table 1, entries 3 and 4).

(12) Wender, P. A.; Hilleman, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205–2208.

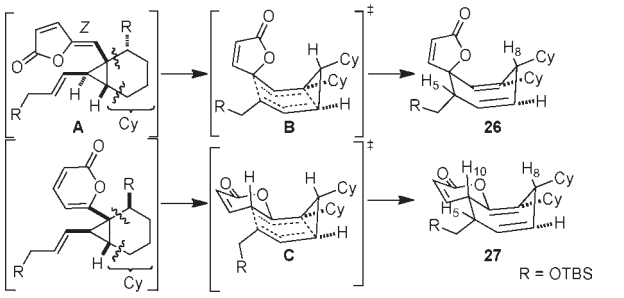
(13) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70* 7679–7685.

(14) Coupling constant for saturated alicyclic cyclopropane: 6 < $^3J_{cis}$ < 12 2 < $^3J_{trans}$ < 9.Pretsch, E.; Bühlman, P.; Badertscher, M. In *Structure Determination of Organic Compounds*, 4th ed.; Springer-Verlag: Berlin, 2009.

(15) The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 849199).

(16) Inack-Ngi, S.; Rahmani, R.; Commeiras, L.; Chouraqui, G.; Thibonnet, J.; Duchêne, A.; Abarbri, M.; Parrain, J.-L. *Adv. Synth. Catal.* **2009**, *351*, 779–788.

Scheme 4. Hypothetical Transition States



It is worth noting that only one diastereomer has been isolated whatever the path taken (5-*exo*- or 6-*endo*-*dig*), and this could be explained as follows. Since the *Z* exo double bond can be expected from the 5-*exo*-*dig* lactonization **A**[10a] and due to the requirement of a boat transition state for the Cope rearrangement of the divinylcyclopropane intermediate (transition states **B** and **C**, Scheme 4),[11a,17] the two stereogenic centers in **23** and **24** would be formed with complete control of relative stereochemistry. Moreover, the stereochemistry was confirmed and assigned based on NOE NMR experiments (NOEs between H_5-H_{10} and H_8-H_{10} were observed for compound **24**, Table 1).

To summarize, the ABC core of lancifodilactone F (**1**) and schinalactone B (**5**) has been reached via a new domino reaction involving three different steps in the same pot in 31% yield, namely, 68% yield per step.

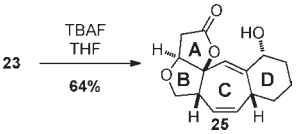
During this ring expansion sequence, three single bonds and two stereogenic centers including a quaternary carbon atom were created with total diastereoselectivity. This approach afforded the initially reported relative stereochemistry at C-5, C-8, and C-10 of the ABC core of lancifodilactone F (**1**).

Regarding the 6-*endo*-*dig* lactonization pathway, this provides an easy access to the (6,7) polyoxygenated bicyclic skeleton. The C-ring enol ether could be further used to install the required C-9 (see **2**–**4**) tertiary alcohol via an α-oxidation.

Finally, substructure **7** was reached by treating **23** with a solution of tetrabutyl ammonium fluoride in THF (Scheme 5). The latter evolved, by an oxa-Michael addition, into the lactone **25** affording the ABCD skeleton of molecules

(17) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203–5223.

Scheme 5. Access to the ABCD Skeleton



isolated from the *Schisandra* genus (**2**, **3**, and **4**) in 64% with concomitant deprotection of the secondary alcohol.

Access to the ABC core of micrandilactone A and lancifodilactone G[8a,e,g] has already been described, but it is worth noting that our strategy represents the first reported synthesis of the ABCD skeleton core of those natural products. Such an approach allowed us to install diastereoselectively four stereocenters.

Being able to reach different substructures of molecules belonging to the same family (Figure 1, highlighted in red) from one common intermediate **23** shows the inherent flexibility of this new method. Following the example of nature during biosynthesis, this new domino cascade reaction can follow different paths depending on the nature of the diastereomer **22** used.

In conclusion, a convergent and versatile route to the diastereomeric scaffold of molecules isolated from the genus *Schisandra* has been elaborated. Key elements of the sequence include a one-pot cascade which sequentially forged three rings and a quaternary spirocenter to complete the ABC core of the lancifodilactone F. A hetero-Michael reaction fashions the final B ring of molecules related to micrandilactone B. This collective domino approach allowed the formation of those complex natural products in less than 13 steps. From this new synthetic tool will evolve new synthetic strategies toward complex natural products from the genus *Schisandra*.

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Supporting Information Available. Experimental procedures and characterization for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.