Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201605879
German Edition: DOI: 10.1002/ange.201605879

Total Synthesis of the Diterpenoid (+)-Harringtonolide

*Hai-Jun Zhang[+], Lin Hu[+], Zhiqiang Ma, Ruining Li, Zhen Zhang, Cheng Tao, Bin Cheng, Yun Li, Huifei Wang, and Hongbin Zhai**

In memory of Nanjun Sun and Puzhu Cong

Abstract: *Described herein is the first asymmetric total synthesis of (+)-harringtonolide, a natural diterpenoid with an unusual tropone imbedded in a cagelike framework. The key transformations include an intramolecular Diels–Alder reaction and a rhodium-complex-catalyzed intramolecular [3+2] cycloaddition to install the tetracyclic core as well as a highly efficient tropone formation.*

The structurally unique diterpenoid (+)-harringtonolide (**1**; Figure 1) was first isolated from the seeds of *Cephalataxus harringtonia* by Buta and co-workers in 1978,[1a] and subsequently from the bark of the Chinese species *Cephalotaxus hainanensis* by Sun et al. in 1979, yet under the name of hainanolide.[1b] Hainanolidol (**2**), the structural congener of hainanolide was also isolated.[1b] The cagelike diterpenoid **1** contains an unusual tropone ring, a compact *cis*-fused tricyclic ring system carrying seven contiguous stereogenic centers, a bridged lactone, and a tetrahydrofuran ring. (+)-Harringtonolide (**1**) was shown to inhibit the growth of tobacco and beans and to be antineoplastically and antivirally active. In addition, it was found to have potent cytotoxic activities with an $IC_{50} = 43$ nM for KB tumor cells and to cause necrosis under certain conditions.[2] In contrast, **2** was biologically inactive,[2,3] thus suggesting that the THF ring in **1** might play a decisive role in its biological activity. The chemical relationship between the two natural products was investigated, as exemplified by a biomimetic transformation of **2** into **1** through an oxidation process promoted by lead tetraacetate, though the yield was not given in the literature.[4]

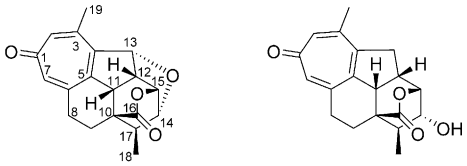


Figure 1. The cephalotaxus norditerpenes **1** and **2**.

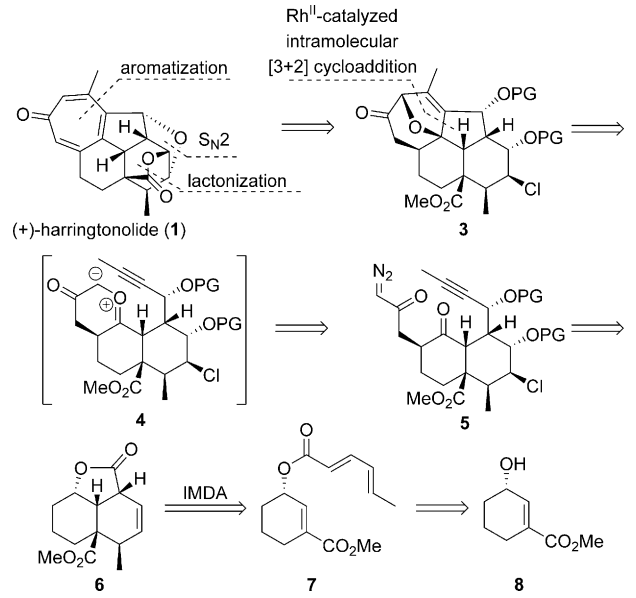
Owing to their intriguing architecture and outstanding biological activities, **1** and its derivatives have attracted considerable attention from the synthetic community. Many synthetic efforts have been devoted to **1** since its isolation.[5–8] In 1998, Mander's group demonstrated a groundbreaking total synthesis of (±)-hainanolidol, which constituted a formal synthesis of **1**.[6g] The elegant strategy featured arene cyclopropanation and a subsequent ring expansion for the construction of the tropone moiety, though the formation of the THF ring of the natural product at an early stage proved to be unfavorable.[6d–f] More recently, Tang et al. reported an efficient total synthesis of **1** through an intramolecular oxidopyrylium-based [5+2] cycloaddition to assemble the tetracyclic carbon skeleton.[9] Nevertheless, the asymmetric synthesis of this molecule has not been accomplished to date. As part of our long-term efforts on streamlining efficient synthetic strategies for complex natural products, we present herein the first enantioselective total synthesis of (+)-harringtonolide (**1**).

The retrosynthetic analysis is outlined in Scheme 1. We envisioned that the construction of the tropone, the lactone, and the ether ring moieties in **1** could be achieved by a sequence of late-stage functionalizations from the oxapentacyclic derivative **3**. In a key synthetic step, **3** could be constructed through an intramolecular [3+2] cycloaddition of the intermediate **4**, generated in situ from the diazo intermediate **5** and a rhodium(II) catalyst.[10] The diazo **5**, with correct configuration of the stereochemical centers and all associated functional groups, may be obtained from the compound **6**, having 6-6 *cis*-fused rings, which in turn could be derived from the ester **7** through an intramolecular Diels–Alder reaction. Finally, **7** could be disconnected into the known compound **8**.[11]

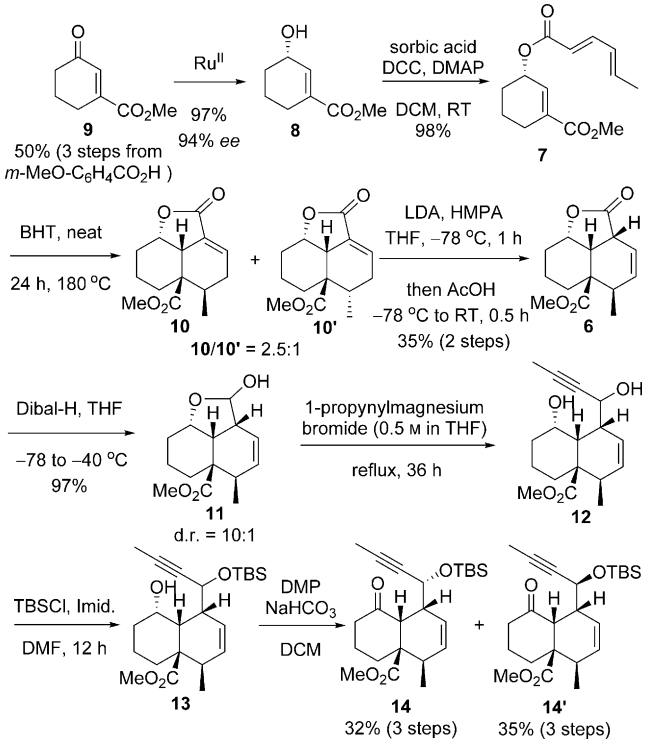
As delineated in Scheme 2, our synthesis began with the enone **9**, a known compound accessible from 3-methoxybenzoic acid in three steps (see the Supporting Information).

[*] H.-J. Zhang,[+] Z. Zhang, C. Tao, Dr. B. Cheng, Dr. Y. Li, Prof. Dr. H. Zhai
The State Key Laboratory of Applied Organic Chemistry
College of Chemistry and Chemical Engineering
Lanzhou University
222 Tianshui South Road, Lanzhou 730000 (China)
E-mail: zhaihb@pkusz.edu.cn
Dr. H. Wang, Prof. Dr. H. Zhai
Guangdong Provincial Key Laboratory of Nano-Micro Materials Research, Key Laboratory of Chemical Genomics
Shenzhen Graduate School of Peking University
Shenzhen 518055 (China)
Dr. L. Hu,[+] Dr. Z. Ma, Dr. R. Li, Prof. Dr. H. Zhai
CAS-Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, Shanghai 200032 (China)
Prof. Dr. H. Zhai
Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, Tianjin 300071 (China)
[+] These authors contributed equally.

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201605879.



Scheme 1. Retrosynthetic analysis of (+)-harringtonolide (**1**). PG = protecting group.

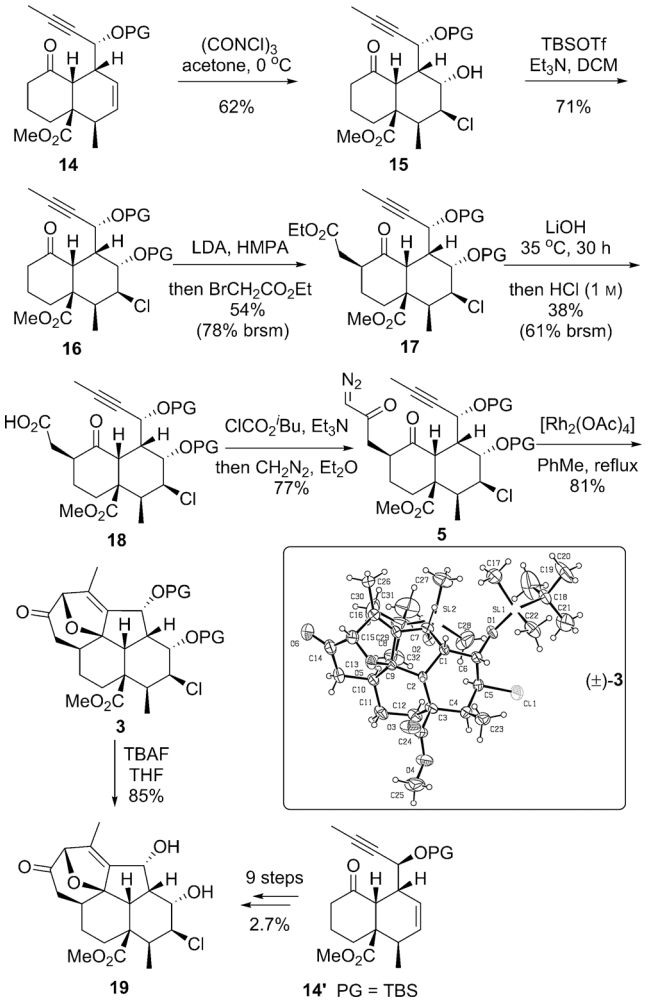


Scheme 2. Synthesis of the intermediates **14** and **14′**. BHT = 2,6-di-*tert*-butyl-*p*-cresol, DCC = dicyclohexylcarbodiimide, DCM = dichloromethane, Dibal-H = diisobutylaluminum hydride, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMP = Dess–Martin periodinane, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, "Ru^{II}" = [RuCl(*p*-cymene){(*S*,*S*)-Ts-DPEN}], TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

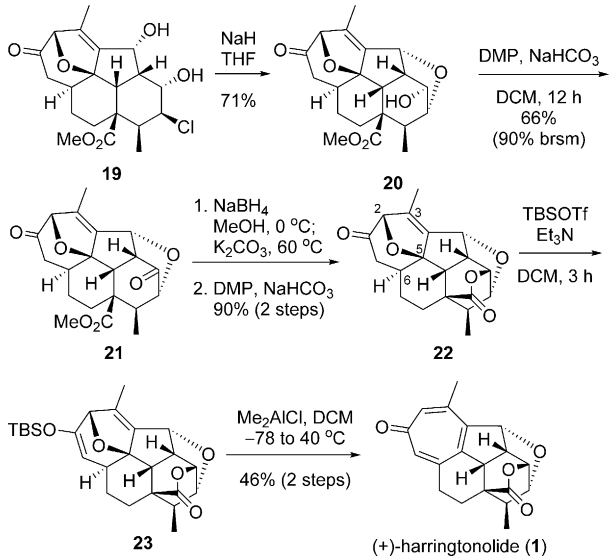
Asymmetric reduction of **9** was achieved by a hydride transfer hydrogenation catalyzed by [RuCl(*p*-cymene){(*S*,*S*)-Ts-DPEN}], thus providing the corresponding allylic alcohol **8** in up to 94% *ee* and 97% yield.[11] Condensation of **8** and sorbic acid afforded ester **7**. To our delight, the key intramolecular Diels–Alder reaction and the subsequent spontaneous C=C bond shift proceeded smoothly at 180 °C in the presence of the polymerization inhibitor BHT to afford a diastereomeric mixture of **10** and **10′** in a 2.5:1 ratio.[12] However, the major *endo* compound **10** in the mixture cannot be separated by either column chromatography or recrystallization at this stage. Thus, **6** was obtained by treatment of the diastereomers with LDA and HMPA at −78 °C followed by quenching with AcOH.[13] Selective partial reduction of the lactone moiety in **6** with Dibal-H afforded a mixture of hemiacetals (**11**) in 97% yield. The chemoselectivity for this step presumably arose from the sterically hindered environment of the methoxycarbonyl functionality. After extensive screening of the nucleophilic reagents, it was found that treatment of the above mixture with 1-propynylmagnesium bromide in refluxing THF furnished the propargyl alcohol **12** as a 1:1 diastereomeric mixture. Efforts on optimizing the diastereomeric ratio proved unsuccessful. The hydroxy group at the propargyl position was then protected selectively and the two epimers, **14** and **14′**, were readily separated after oxidation of the unprotected hydroxy group. The configuration of the propargyl alcohol in **14** was in agreement with that of the natural product by the X-ray crystallographic analyses of several advanced intermediates (in the racemic form, see the Supporting Information for details). Although it was difficult to convert **14′** into **14** in this case, the former (**14′**) could be transformed into intermediate **19** in a similar way.

Next, the bicycle **14** was employed to investigate the intramolecular [3+2] cycloaddition (i.e., **5**→**3**, Scheme 3). Preliminary studies[14,15] suggested that the carbon–carbon double bond in **14** should be converted prior to the cycloaddition into a chlorohydrin moiety, and could be used to construct the lactone and THF rings present in the target molecule at a late stage. Thus, **14** was treated with $(CONCl)_3$ (trichloroisocyanuric acid)[16] to afford the chlorohydrin **15** stereo- and regioselectively. The Cl^+ species generated in situ approached the carbon–carbon double bond from the convex face of the 6-6 *cis*-fused rings, and the reactive intermediate thus formed, having a three-membered ring, was subsequently opened up by nucleophilic attack of water from the α-face.

Protection of the hydroxy group in **15** by TBS led to **16**. The side-chain in acyldiazo **5** was constructed through a reaction sequence including alkylation of **16**, saponification of **17**, and activation of **18** followed by reaction with freshly prepared CH_2N_2.[10] It is worth mentioning that only about half of **17** underwent the saponification to yield **18**, and the reaction conditions need to be controlled rigorously, otherwise isomerization of the 6-6 *cis*-fused rings would occur and the number of byproducts would increase substantially.[17] As the stereogenic centers in **5** were in agreement with the natural product, the following key intramolecular [3+2] cycloaddition was carried out to assemble the tetracyclic carbon backbone of the natural product. According to the procedure reported by Schmalz and co-workers,[10] the $[Rh_2(OAc)_4]$-catalyzed [3+2] cycloaddition took place smoothly in refluxing toluene, thus furnishing the oxapentacycle **3** in 81% yield. The structure was partially confirmed by an X-ray



Scheme 3. Construction of the oxapentacycle **19** from **14**. TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl.



Scheme 4. Completion of the total synthesis of (+)-harringtonolide (**1**).

crystallographic analysis of (±)-**3**.[21] Desilylation of **3** with TBAF generated the diol **19**. Similar to bicycle **14**, the epimer **14′** was also utilized to construct **19** (see the Supporting Information for more details).

With **19** secured, the remaining tasks for the total synthesis of **1** were to install the THF ring, the lactone, and the tropone moiety (Scheme 4). The diol **19** was subjected to a NaH-mediated S_N2 reaction, thus furnishing the desired cyclic ether **20** as the major product.[18] To close the lactone ring, the configuration of the remaining hydroxyl group in **20** had to be inverted. Mitsunobu reaction resulted in the recovery of the starting material, possibly because of the steric hindrance present in the molecule. Thus, a redox protocol was employed instead. The compound **20** was oxidized to the dione **21**, reduction and subsequent lactonization of which was realized in a one-pot fashion. Oxidation of the remaining hydroxy group led to the compound **22**, an intermediate possessing the desired skeleton of the natural product.

The endgame for the total synthesis of **1** was the formation of the tropone unit. According to the literature procedure,[10c] cleavage of the C5–O bond, elimination of the proton at C6 (adjacent to the tertiary carbenium at C5), and dehydration involving the hydroxy group at C2 would generate the tropone moiety. In our case, treatment of **22** with Me_2AlCl led to a diene compound.[19] We speculated that preferential elimination of C6–H would eventually favor the tropone formation. Therefore, the carbonyl group within the seven-membered ring had better be converted into an enol ether to further activate the C6–H bond. Based upon the above analysis, exposure of **22** to TBSOTf and Et_3N furnished the silyl enol ether **23**, which was used directly in the next step without further purification. Gratifyingly, the tropone unit was smoothly constructed and the natural product (+)-harringtonolide (**1**) was obtained as the major product upon treatment of the unpurified **23** with Me_2AlCl.[20] The spectroscopic data (HRMS; ^1H and ^{13}C NMR) were fully consistent with those reported for the natural product.[1,9]

In summary, we have developed a novel and concise strategy for the enantioselective total synthesis of (+)-harringtonolide (**1**) in 20 steps from the known alcohol **8**.[11] The key transformations include an asymmetric transfer hydrogenation, an intramolecular Diels–Alder reaction, selective functionalization of the olefin in the presence of an acetylenic group, a rhodium-complex-catalyzed intramolecular [3+2] cycloaddition, and formation of the tropone via a silyl enol ether.

Acknowledgments

We thank the NSFC (21272105; 21290183), Shenzhen Science and Technology Innovation Committee (JCYJ20150529153646078), Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT_15R28), and "111" Program of MOE for financial support. We are grateful to Prof. Fayang Qiu of GIBH for enlightening discussions.

Keywords: asymmetric synthesis · cycloaddition · natural products · terpenoids · total synthesis

[1] a) J. G. Buta, J. L. Flippen, W. R. Lusby, *J. Org. Chem.* **1978**, *43*, 1002 – 1003; b) N. J. Sun, Z. Xue, X. T. Liang, L. Huang, *Acta Pharm. Sin.* **1979**, *14*, 39 – 44.

[2] L. Evanno, A. Jossang, J. Nguyen-Pouplin, D. Delaroche, P. Herson, M. Seuleiman, B. Bodo, B. Nay, *Planta Med.* **2008**, *74*, 870 – 872.

[3] S. Q. Kang, S. Y. Cai, L. Teng, *Acta Pharm. Sin.* **1981**, *16*, 867 – 868.

[4] Z. Xue, N. J. Sun, X. T. Liang, *Acta Pharm. Sin.* **1982**, *17*, 236 – 237.

[5] a) L. Y. Zhang, S. Z. Chen, D. Wei, L. Huang, J. J. Chai, C. H. He, *Chin. Chem. Lett.* **1996**, *7*, 892 – 893; b) L. Y. Zhang, W. Q. Yang, S. Z. Chen, L. Huang, *Chin. Chem. Lett.* **1997**, *8*, 15 – 16; c) W. Q. Yang, L. Y. Zhang, S. Z. Chen, L. Huang, *Chin. Chem. Lett.* **1997**, *8*, 203 – 204; d) W. Q. Yang, X. M. Yu, S. Z. Chen, L. Huang, *Chin. Chem. Lett.* **1997**, *8*, 1043 – 1044; e) Z. Q. Yang, S. Z. Chen, L. Huang, *Chin. Chem. Lett.* **1998**, *9*, 261 – 262; f) X. M. Yu, L. Y. Zhang, S. Z. Chen, L. Huang, *Chin. Chem. Lett.* **1999**, *10*, 657 – 658; g) X. M. Yu, S. Z. Chen, L. Huang, *Chin. Chem. Lett.* **2000**, *11*, 295 – 296; h) Y. W. Li, L. Huang, *Chin. Chem. Lett.* **2002**, *13*, 937 – 938; i) Y. W. Li, L. Y. Zhu, L. Huang, *Chin. Chem. Lett.* **2004**, *15*, 397 – 399.

[6] a) D. H. Rogers, J. C. Morris, F. S. Roden, B. Frey, G. R. King, F. W. Russkamp, R. A. Bell, L. N. Mander, *Pure Appl. Chem.* **1996**, *68*, 515 – 522; b) D. H. Rogers, B. Frey, F. S. Roden, F. W. Russkamp, A. C. Willis, L. N. Mander, *Aust. J. Chem.* **1999**, *52*, 1093 – 1108; c) B. Frey, A. P. Wells, F. Roden, T. D. Au, D. C. Hockless, A. C. Willis, L. N. Mander, *Aust. J. Chem.* **2000**, *53*, 819 – 830; d) H. B. Zhang, D. C. Appels, D. C. R. Hockless, L. N. Mander, *Tetrahedron Lett.* **1998**, *39*, 6577 – 6580; e) L. N. Mander, T. P. O'Sullivan, *Synlett* **2003**, 1367 – 1369; f) T. P. O'Sullivan, H. B. Zhang, L. N. Mander, *Org. Biomol. Chem.* **2007**, *5*, 2627 – 2635; g) B. Frey, A. P. Wells, D. H. Rogers, L. N. Mander, *J. Am. Chem. Soc.* **1998**, *120*, 1914 – 1915.

[7] a) L. Evanno, A. Deville, L. Dubost, A. Chiaroni, B. Bodo, B. Nay, *Tetrahedron Lett.* **2007**, *48*, 2893 – 2896; b) L. Evanno, A. Deville, B. Bodo, B. Nay, *Tetrahedron Lett.* **2007**, *48*, 4331 – 4333; c) H. Abdelkafi, L. Evanno, P. Herson, B. Nay, *Tetrahedron Lett.* **2011**, *52*, 3447 – 3450; d) H. Abdelkafi, L. Evanno, A. Deville, L. Dubost, A. Chiaroni, B. Nay, *Eur. J. Org. Chem.* **2011**, 2789 – 2880; e) H. Abdelkafi, P. Herson, B. Nay, *Org. Lett.* **2012**, *14*, 1270 – 1273; f) H. Abdelkafi, B. Nay, *Nat. Prod. Rep.* **2012**, *29*, 845 – 869.

[8] a) V. Hegde, M. Campitelli, R. J. Quinn, D. Camp, *Org. Biomol. Chem.* **2011**, *9*, 4570 – 4579; b) W. L. Li, *Asian J. Chem.* **2012**, *24*, 1411 – 1412; c) Z. Q. Ma, B. Cheng, H. B. Zhai, *Asian J. Org. Chem.* **2014**, *3*, 1097 – 1103.

[9] M. Zhang, N. Liu, W. P. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 12434 – 12438.

[10] a) T. Graening, W. Friedrichsen, J. Lex, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2002**, *41*, 1524 – 1526; *Angew. Chem.* **2002**, *114*, 1594 – 1597; b) M. C. McMills, D. L. Wright, R. M. Weekly, *Synth. Commun.* **2002**, *32*, 2417 – 2425; c) T. Graening, V. Bette, J. Neudörfl, J. Lex, H.-G. Schmalz, *Org. Lett.* **2005**, *7*, 4317 – 4320.

[11] a) T. Ikariya, S. Hashiguchi, K. Murata, R. Noyori, *Org. Synth.* **2005**, *82*, 10 – 17; b) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285 – 288; *Angew. Chem.* **1997**, *109*, 297 – 300; c) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562 – 7563.

[12] S. Chackalamannil, Y. Xia, W. J. Greenlee, M. Clasby, D. Doller, H. Tsai, T. Asberom, M. Czarniecki, H.-S. Ahn, G. Boykow, C. Foster, J. Agans-Fantuzzi, M. Bryant, J. Lau, M. Chintala, *J. Med. Chem.* **2005**, *48*, 5884 – 5887.

[13] a) B. M. Trost, T. A. Grese, *J. Am. Chem. Soc.* **1991**, *113*, 7363 – 7372; b) A. S. Kende, B. H. Toder, *J. Org. Chem.* **1982**, *47*, 163 – 167.

[14] We attempted to construct the lactone and THF rings in a one-step fashion in the presence of $Yb(OTf)_3$ after the carbon – carbon bond was converted into epoxypropane stereochemically according to the literature,[7e] but a γ-lactone rather than a δ-lactone was constructed on the tetracyclic carbon skeleton (**A**). The X-ray structural data was deposited at the Cambridge Crystallographic Data Centre. CCDC 1456997 (**A**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See the Supporting Information for details.

[15] We attempted to construct the THF ring on the tetracyclic carbon skeleton after the formation of the tropone moiety. However, a four-membered cyclic ether ring was obtained (**B**). The X-ray structural data was deposited at the Cambridge Crystallographic Data Centre. CCDC 1457121 (**B**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See the Supporting Information for details.

[16] M. Wengert, A. M. Sanseverino, M. C. S. Mattos, *J. Braz. Chem. Soc.* **2002**, *13*, 700 – 703.

[17] To obtain structural information for the byproducts of the saponification step, a [3+2] cycloaddition product was obtained (**C**). The X-ray structural data was deposited at the Cambridge Crystallographic Data Centre. CCDC 1457120 (**C**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See the Supporting Information for details.

[18] The epoxypropane compound **D** was obtained as a byproduct in 14% yield. See the Supporting Information for more details.

[19] The structure of the byproduct was considered to be **E**. See the Supporting Information for more details.

[20] The mechanism for the formation of the tropone was proposed in the Supporting Information.

[21] CCDC 1457123 (**3**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

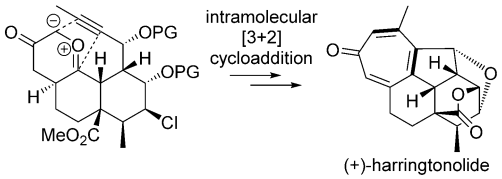
Received: June 17, 2016
Published online: ■■ ■■, ■■■■

Communications

Natural Product Synthesis

H.-J. Zhang, L. Hu, Z. Ma, R. Li, Z. Zhang, C. Tao, B. Cheng, Y. Li, H. Wang, H. Zhai* _____ ■■■■–■■■■

Total Synthesis of the Diterpenoid (+)-Harringtonolide



Ever more rings: The first asymmetric total synthesis of the diterpenoid (+)-harringtonolide is described. The key features include an asymmetric transfer hydrogenation, an intramolecular Diels–Alder reaction, chemoselective functionalization of an olefin in the presence of an acetylenic group, a rhodium-catalyzed intramolecular [3+2] cycloaddition, and efficient formation of the tropone.