ChemComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC04351E

ChemComm

COMMUNICATION

Asymmetric synthesis of the fully functionalized six-membered ring of trigoxyphin A

Received 00th January 20xx,

Jing Feng,[a] Tianzi Yu,[a] Zhijiang Zhang,[a] Jinpeng Li,[a] Shaomin Fu,[a] Juan Chen,[b] and Bo Liu *[a]

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Asymmetric synthesis of the fully functionalized six-membered ring of trigoxyphin A, a daphnane-type diterpenoid, has been accomplished concisely from *D*-tartrate derivative. Key elements of this synthesis involve the tandem ozonization/intramolecular HWE reaction to construct the α,β-unsaturated cyclohexenone skeleton, the radical cyclization to introduce the C8 chirality and sequential Kumada cross-coupling/hydroboration-oxidation to introduce the C11 chirality. The target substructure could be synthetically achieved in a multi-gram scale.

The daphnane diterpene orthoesters (DDOs) are a large family of natural products isolated from the plant families of Thymelaeaceae and Euphorbiaceae. By the end of 2017, about 260 unique members had been identified.[1,2] Many DDOs exhibit remarkable biological activities, such as activation of transient receptor potential vanilloid 1 (TRPV1)[3], anticancer[4], insecticidal[5], and acaricidal[6] activities. These natural products embrace a highly functionalized *trans*,*trans*-fused 5/7/6 (ABC-ring) skeleton containing the 9,13,14-orthoester motif at ring C. Further studies on the structure-activity relationship (SAR) of biologically active DDOs have revealed that the orthoester group may act as an essential pharmacophore.[1a] Trigoxyphin A (**1**, Fig. 1), a representative member of the DDOs, was isolated from twigs of *Trigonostemon xyphophylloides* (Euphorbiaceae) in 2010 by Yue's group.[2a] Different from other DDOs identified before, trigoxyphin A bears an *α*-oriented oxygen substitution at C12. Cytotoxic experiments have demonstrated that trigoxyphin A exhibits high activity against HL60 human leukemia cells and moderate activity against A549 human lung adenocarcinoma cells with IC_{50} values of 0.27 μM and 7.5 μM respectively.

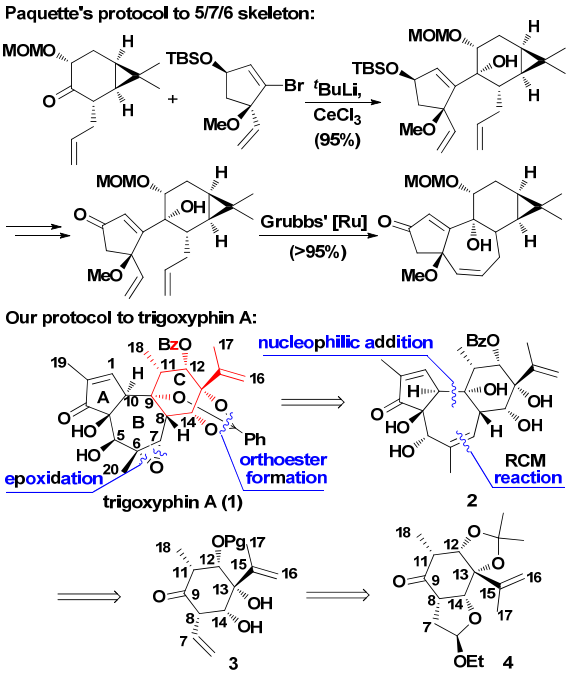


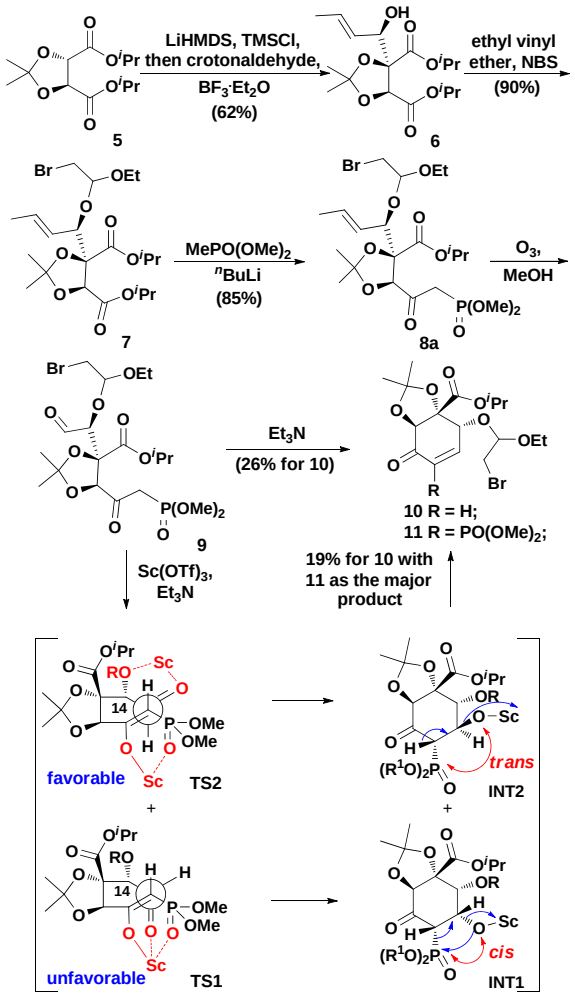
Fig. 1 Paquette's protocol to 5/7/6 skeleton and our protocol to trigoxyphin A

Captivated by their complex molecular structure and diverse biological activities, the synthetic community has devoted numerous endeavors into developing creative approaches to the DDOs. Besides a number of remarkable strategies to the 5/7/6 tricyclic skeleton documented,[7] the first total synthesis of resiniferatoxin[8] was accomplished by Wender's group in 1997 via intramolecular 1,3-dipolar cycloaddition and zirconium-mediated cyclization to forge the scaffold,[9] and the second total synthesis was achieved by Inoue's group in 2017[10]

[a] Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China.
[b] Analytical & Testing Center, Sichuan University, Chengdu 610064, P. R. China.
† Electronic Supplementary Information (ESI) available: experimental details and characterization data for all new compounds. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8CC04351E

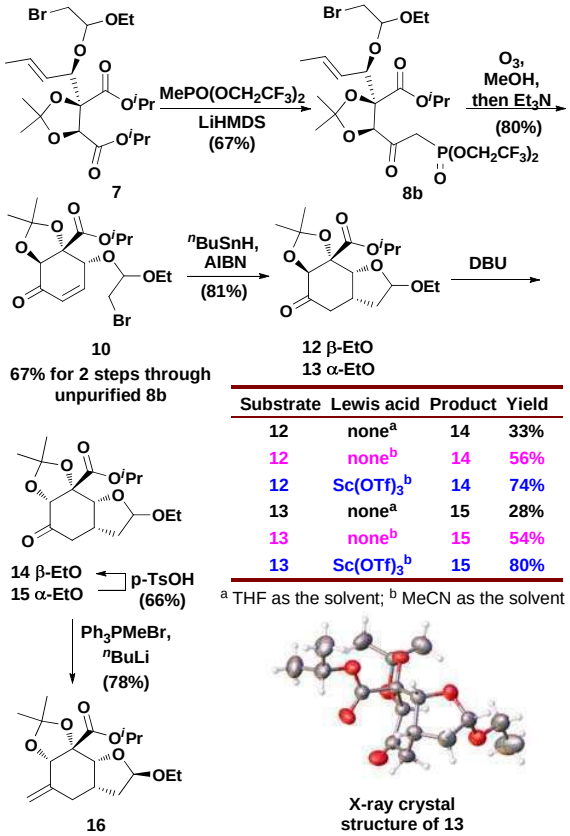
featuring radical-mediated three-component coupling and 7-endo cyclization. Moreover, C6, C7-*epi*-yuanhuapin, an epimer of yuanhuapin which is a natural analog of resiniferatoxin, was synthetically conquered by Wender and co-workers in 2011.[11] As for the construction of the six-membered ring of resiniferatoxin, Inoue's RCM/olefin isomerization strategy has provided a practical access.[7p,10] All these remarkable works provide viable pathways to the DDOs or the related unexplored analogs.



Scheme 1. Synthesis of compound **10**

Inspired by Paquette's work (Fig. 1),[12] which utilized a nucleophilic addition/RCM strategy to forge the 5/7/6 skeleton, we became fascinated by developing a convergent strategy toward DDOs including trigoxyphin A. Synthetically, selective formation of 9,13,14-orthoester,[13] epoxidation and inversion of the chirality of 5-OH from the ABC ring skeleton **2**, a potential synthetic precursor of trigoxyphin A, would furnish the target molecule (Fig. 1). Then we conceived a prudent protocol through RCM strategy to disassemble compound **2** into two highly functionalized segments, i.e. the ring A substructure and the ring C substructure. Structurally, the ring C subunit (compound **3**) bears five contiguous stereogenic centers, two of which are adjacent to the carbonyl and thus facile to experience isomerization. Thus the synthesis of the ring C subunit is challenging on account of its highly functionalized and labile structure. Hence, compound **4**, with a fused 5/6 bicyclic scaffold stabilizing its all-*cis* configuration, was selected as the synthetic surrogate of compound **3** in accordance with both structural stability and synthetic practicality. Herein we present our synthetic endeavors toward compound **4**.

Synthesis of **4** commenced with the BF_3-mediated Mukaiyama aldol reaction (Scheme 1).[14] Reaction of the known compound **5**,[15] with crotonaldehyde, provided compound **6** in 62% yield (dr 25:1). The resultant hydroxy was then protected as an acetal by ethyl vinyl ether and NBS to result in compound **7**. To achieve α,β-unsaturated cyclohexenone from β-keto phosphonates,[16] we exposed **7** to an anion, generated from dimethyl methylphosphonate and ^{n}BuLi, delivering **8a** in 85% yield.[17] Then we set about conducting the tandem ozonization/intramolecular HWE reaction. While initial optimization of a number of bases, solvents and Lewis acid/Lewis base combinations[18] gave no satisfactory results, the weak base Et_3N afforded the desired compound **10** in 26% yield, along with a number of unidentified compounds. Although the combination of $Sc(OTf)_3$ and Et_3N (1:2.5) made the reaction much cleaner than Et_3N alone, compound **10** could only be delivered in 19% yield, along with the undesired compound **11**[19] as the major product



Substrate	Lewis acid	Product	Yield
12	none[a]	14	33%
12	none[b]	14	56%
12	$Sc(OTf)_3$[b]	14	74%
13	none[a]	15	28%
13	none[b]	15	54%
13	$Sc(OTf)_3$[b]	15	80%

[a] THF as the solvent; [b] MeCN as the solvent

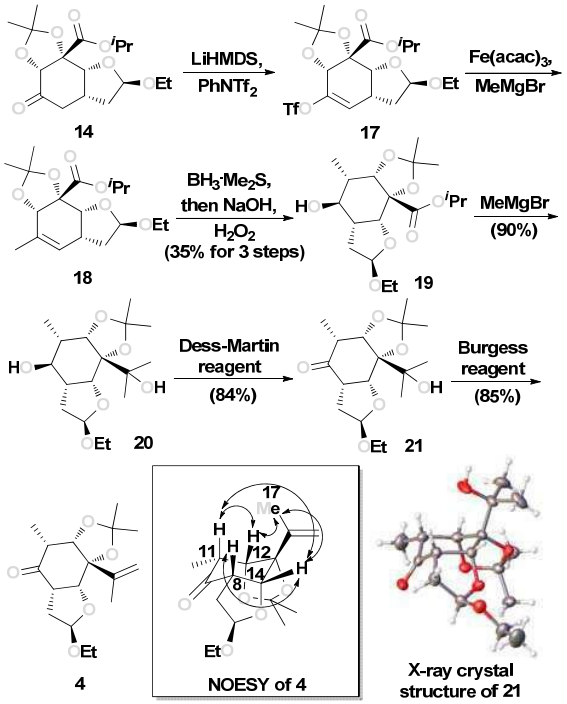
Scheme 2. Synthesis of compound **16**

View Article Online
DOI: 10.1039/C8CC04351E

through Knoevenagel condensation. The chelation of C14-OR, $Sc(OTf)_3$ and the aldehyde made TS2 the favorable transient state and delivered Knoevenagel condensation product **11**.

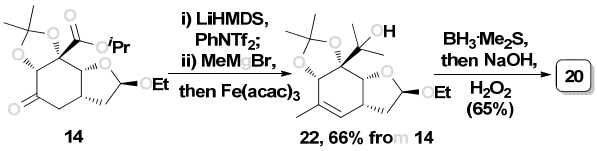
With these negative results, we inferred that modification of the β-keto phosphonate **8a** into the *bis*(trifluoroethyl) phosphonoketone **8b** might prompt the elimination step in the desired HWE process (Scheme 2).[20] Accordingly, exposure of the aldehyde intermediate, obtained after ozonization, to Et_3N boosted the desired α,β-unsaturated ketone **10** in 80% yield. Notably, synthetic access to compound **8b** required quick transfer of LiHMDS (keeping at -78°C) to the mixed solution of the *bis*(trifluoroethyl) methylphosphonate and compound **7** at -78 °C.[21] Further treatment of the acetal **10** with *tri-n*-butyltin hydride in the presence of azobisisobutyronitrile[22] successfully afforded the bicycle **12** and **13** in the ratio of 1.2:1, as determined by ^{1}H NMR. The stereochemistry of compound **13** was confirmed by X-ray crystallography.[23] **12** and **13** were separated and then subjected to stereochemical inversion at C12 to achieve the thermodynamically more stable product **14** and **15** respectively. Sole utilization of DBU[24] in THF only led to **14** and **15** in 33% and 28% yield respectively. Switching from THF to MeCN as the solvent resulted in higher yields (56% and 54% for **14** and **15** respectively). More pleasingly, optimal combination of DBU/$Sc(OTf)_3$[25] (8:1) delivered compounds **14** and **15** in 74% and 80% yield respectively. Treating **15** under *p*-TsOH fulfilled its conversion into **14** in 66% yield.[26] Wittig olefination of **14** afforded compound **16** in 78% yield.

Both allylic oxidation and isomerization of the *exo* double bond into the *endo* position in compound **16** failed, which made us to resort to alternative tactics to access compound **4**. Thus, regioselective enolization of the ketone **14** at the less hindered site and further treatment with $PhNTf_2$ furnished the triflic enol ester **17** (Scheme 3). Iron-catalyzed Kumada-coupling between **17** with and MeMgBr in the presence of NMP afforded **18**,[27] which then underwent hydroboration-oxidation to produce the alcohol **19** in 35% yield over 3 steps. Notably, the degradative product of $PhNTf_2$[28] made it tough for purification of **17** and **18**,[29] so we could not calculate the exact yields until formation of **19**. Subsequent Grignard addition and Dess-Martin oxidation provided compound **21** smoothly. The stereochemistry of compound **21** was confirmed by X-ray crystallography. Final elimination of the tertiary hydroxyl with Burgess reagent furnished compound **4**.[30] The relative configuration of compound **4** was established by NOESY correlations of H11/H12, H11/H14, H12/H17, H14/H17 and H8/H14.



Scheme 3. Synthesis of compound **4**

Because both the Kumada coupling from **17** to **18** and the Grignard addition from **19** to **20** utilized methylmagnesium bromide (Scheme 3), we envisioned the synthetic route from **14** to **20** could be simplified. Pleasingly, treatment of the crude compound **17**, generated from **14**, with excess MeMgBr and subsequent addition of catalytic $Fe(acac)_3$ led to the olefin **22** in 66% yield over two steps (Scheme 4). Then hydroboration-oxidation reaction successfully gave rise to the alcohol **20** in 65% yield.[31]



Scheme 4. Alternative synthesis of compound **20**

In summary, we have reported a concise and asymmetric synthesis toward the fully functionalized six-membered ring of trigoxyphin A. Protections of dihydroxyl group (C_{12}, C_{14}) as acetals were devised to minimize undesired β-elimination. The synthesis features direct introduction of the stereogenic centers at C12 and C13 from the cheap starting material, generation of the C14 stereogenic center via Mukaiyama aldol reaction, construction of α,β-unsaturated cyclohexenone through tandem ozonization/intramolecular HWE, and radical cyclization and hydroboration-oxidation to introduce the C8 and C11 stereogenic centers. Further synthetic extension to trigoxyphin A and other related daphnane diterpene orthoesters (DDOs) is on progress in our laboratory.

Acknowledgements

We acknowledge financial support from the National Natural Science Foundation of China (21672153 and 21290180), and the Fundamental Research Funds for the Central Universities (2012017yjsy148). We also thank the Analytical & Testing Center of Sichuan University for NMR and X-Ray recording.

Conflicts of interest

There are no conflicts to declare.

View Article Online
DOI: 10.1039/C8CC04351E

Notes and references

1 For recent reviews on daphnane diterpene orthoesters, see: *(a)* S.-G. Liao, H.-D. Chen and J.-M. Yue, *Chem. Rev.,* 2009, **109**, 1092; *(b)* H.-B. Wang, L.-P. Liu and X.-Y. Wang, *Magn. Reson. Chem.,* 2013, **51**, 580.

2 For the isolations of trigoxyphins and other structure-related DDOs from 2009, see: (*a*) B.-D. Lin, M.-L. Han, Y.-C. Ji, H.-D. Chen, S.-P. Yang, S. Zhang, M.-Y. Geng and J.-M. Yue, *J. Nat. Prod.,* 2010, **73***,* 1301; (*b*) S.-H. Dong, H.-B. Liu, C.-H. Xu, J. Ding and J.-M. Yue, *J. Nat. Prod.,* 2011, **74**, 2576; (*c*) S.-F. Li, Y.-T. Di, S.-L. Li, Y. Zhang, F.-M. Yang, Q.-Y. Sun, J. M. Simo, H.-P. He and X.-J. Hao, *J. Nat. Prod.,* 2011, **74**, 464; (*d*) B. Yang, G.-Y. Chen, X.-P. Song, L.-Q. Yang, C.-R. Han, X.-Y. Wu, X.-M. Li and B.-Y. Zou, *Bioorg. Med. Chem. Lett.,* 2012, **22**, 3828; (*e*) Y.-Y. Cheng, H. Chen, H.-P. He, Y. Zhang, S.-F. Li, G.-H. Tang, L.-L. Guo, W. Yang, F. Zhu, Y.-T. Zheng, S.-L. Li and X.-J. Hao, *Phytochemistry* 2013, **96**, 360; (*f*) L. Yu, W.-J. Zuo, W.-L. Mei, Z.-K. Guo, X.-N. Li and H.-F. Dai, *Phytochemistry Lett.,* 2013, **6**, 472; (*g*) M. Bourjot, P. Leyssen, J. Neyts, V. Dumontet and M. Litaudon, *Molecules* 2014, **19**, 3617; (*h*) B. Yang, Z. Meng, Z. Li, L. Sun, Y. Hu, Z. Wang, G. Ding, W. Xiao and C. Han, *Phytochemistry Lett.,* 2015, **11**, 270.

3 (*a*) M. J. Caterina, M. A. Schumacher, M. Tominaga, T. A. Rosen, J. D. Levine and D. Julius, *Nature* 1997, **389**, 816; (*b*) A. Szallasi and P. M. Blumberg, *Pharmacol. Rev.,* 1999, **51**, 159.

4 (*a*) G. Rovera, T. G. O'Brien and L. Diamond, *Science* 1979, **204**, 868; (*b*) L. Saraiva, P. Fresco, E. Pinto, H. Portugal and J. Goncalves, *Planta Med.,* 2001, **67**, 787.

5 (*a*) A. E. Bala, R. Delorme, A. Kollmann, L. Kerhoas, J. Einhorn, P.-H. Ducrot and D. Auge, *Pestic. Sci.* 1999, **55**, 745; (*b*) A. Sogabe, K. Kinjo, F. Abe, T. Yamauchi and S. Yaga, *Mokuzai Gakkaishi* 2000, **46**, 47; *Chem. Abstr.,* 2000, **133**, 165277; (*c*) H. Jayasuriya, D. L. Zink, S. B. Singh, R. P. Borris, W. Nanakorn, H. T. Beck, M. J. Balick, M. A. Goetz, L. Slayton, L. Gregory, M. Zakson-Aiken, W. Shoop and S. B. Singh, *J. Am. Chem. Soc.,* 2000, **122**, 4998.

6 N. Soonthornchareonnon, M. Sakayarojkul, M. Isaka, V. Mahakittikun, W. Chuakul and P. Wongsinkongman, *Chem. Pharm. Bull.* 2005, **53**, 241.

7 (*a*) P. A. Wender, H. Y. Lee, R. S. Wilhelm and P. D. Williams, *J. Am. Chem. Soc.,* 1989, **111**, 8954; (*b*) P. A. Wender and F. E. McDonald, *J. Am. Chem. Soc.,* 1990, **112**, 4956; (*c*) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas and D. Watkin, *J. Chem. Soc., Chem. Commun.,* 1990, 605; (*d*) P. A. Wender and F. E. McDonald, *Tetrahedron Lett.,* 1990, **31**, 3691; (*e*) P. C. B. Page, D. C. Jennens, R. A. Porter and A. N. Baldock, *Synlett.,* 1991, 472; (*f*) P. A. Wender and J. L. Mascarenas, *J. Org. Chem.,* 1991, **56**, 6267; (*g*) P. C. B. Page and D. C. Jennens, *J. Chem. Soc., Perkin. Trans. 1,* 1992, 2587; (*h*) M. C. McMills, L. Zhuang, D. L. Wright and W. Watt, *Tetrahedron Lett.,* 1994, **35**, 8311; (*i*) P. C. B. Page, D. C. Jennens and H. McFarland, *Tetrahedron Lett.,* 1997, **38**, 5395; (*j*) K. Lee and J. K. Cha, *Org. Lett.,* 1999, **1**, 523; (*k*) G. L. Carroll and R. D. Little, *Org. Lett.,* 2000, **2**, 2873; (*l*) S. R. Jackson, M. G. Johnson, M. Mikami, S. Shiokawa and E. M. Carreira, *Angew. Chem., Int. Ed.* 2001, **40**, 2694; (*m*) P. C. B. Page, C. M. Hayman, H. L. McFarland, D. J. Willock and N. M. Galea, *Synlett.,* 2002, 583; (*n*) P. A. Wender, F. C. Bi, N. Buschmann, F. Gosselin, C. Kan, J.-M. Kee and H. Ohmura, *Org. Lett.,* 2006, **8**, 5373; (*o*) C. Stewart, R. McDonald and F. G. West, *Org. Lett.,* 2011, **13**, 720; (*p*) K. Murai, S. Katoh, D. Urabe and M. Inoue, *Chem. Sci.,* 2013, **4**, 2364; (*q*) A. J. Catino, A. Sherlock, P. Shieh, J. S. Wzorek and D. A. Evans, *Org. Lett.,* 2013, **15**, 3330; (*r*) G. Tong, Z. Liu, and P. Li, *Org. Lett.,* 2014, **16**, 2288; (*s*) A. H. E. Hassan, J. K. Lee, A. N. Pae, S.-J. Min and Y. S. Cho, *Org. Lett.,* 2015, **17**, 2672; (*t*) Y. Li, M. Wei and M. Dai, *Tetrahedron* 2017, **73**, 4172; (u) R. Liu, J. Feng and B. Liu, *Acta Chim Sinica* 2016, **74**, 24.

8 M. Hergenhahn, W. Adolf and E. Hecker, *Tetrahedron Lett.,* 1975, **16**, 1595.

9 P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe and Y. Ueno, *J. Am. Chem. Soc.,* 1997, **119,** 12976.

10 S. Hashimoto, S. Katoh, T. Kato, D. Urabe and M. Inoue, *J. Am. Chem. Soc.,* 2017, **139**, 16420.

11 P. A. Wender, N. Buschmann, N. B. Cardin, L. R. Jones, C. Kan, J.-M. Kee, J. A. Kowalski and K. E. Longcore, *Nat. Chem.,* 2011, **3**, 615.

12 L. A. Paquette, F. Gallou, Z. Zhao, D. G. Young, J. Liu, J. Yang and D. Friedrich, *J. Am. Chem. Soc.,* 2000, **122**, 9610.

13 W. He, M. Cik, G. Appendino, L. V. Puyvelde, J. E. Leysen and N. De Kimpe, *Mini-Rev. Med. Chem.,* 2002, **2**, 185.

14 V. K. Aggarwal, S. J. Masters, H. Adams, S. E. Spey, G. R. Brown and A. J. Foubister, *J. Chem. Soc., Perkin Trans. 1,* 1999, 155.

15 S. Saito, O. Narahara, T. Ishikawa, M. Asahara, T. Moriwake, J. Gawronski and F. Kazmierczak, *J. Org. Chem*., 1993, **58**, 6292.

16 R. D. Clark, L. G. Kozar and C. H. Heathcock, *Synth. Commun.*, 1975, **5**, 1.

17 E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.,* 1966, **88**, 5654.

18 (*a*) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.,* 1984, **25**, 2183; *(b)* K. Ando, T. Oishi, M. Hirama, H. Ohno and T. Ibuka, *J. Org. Chem.* 2000, **65**, 4745.

19 The TLC of the reaction showed only two products with almost 100% conversion of intermediate **9**. The Knoevenagel condensation product (**11**) was failed to be purified, but the high resolution mass spectrum (HRMS) of the crude proved this product.

20 A. A. Davis, J. J. Rosen and J. J. Kiddle, *Tetrahedron Lett.,* 1998, **39**, 6263.

21 K. Molnár, L. Takács, M. Kádár, F. Faigl and Z. Kardos, *Tetrahedron Lett.,* 2015, **56**, 4877.

22 (*a*) G. Stork, R. Mook, S. A. Biller and S. D. Rychnovsky, *J. Am. Chem. Soc.,* 1983, **105**, 3741; (*b*) G. Stork and P. M. Sher, *J. Am. Chem. Soc.,* 1986, **108**, 303.

23 The configuration of acetal of compound **12** could not be perfectly confirmed by the NOESY and it could only be proved indirectly by the X-ray crystal structure of **13**.

24 R. Mohanrao, A. Asokan and K. M. Sureshan, *Chem. Commun.,* 2014, **50**, 6707.

25 L. Yang, J. Feng, J. Li and B. Liu, *Tetrahedron Lett.,* 2015, **56**, 4931.

26 C. G. Kruse, E. K. Poels, F. L. Jonkers and A. van der Gen, *J. Org. Chem.,* 1978, **43**, 3548.

27 B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.,* 2004, **69**, 3943.

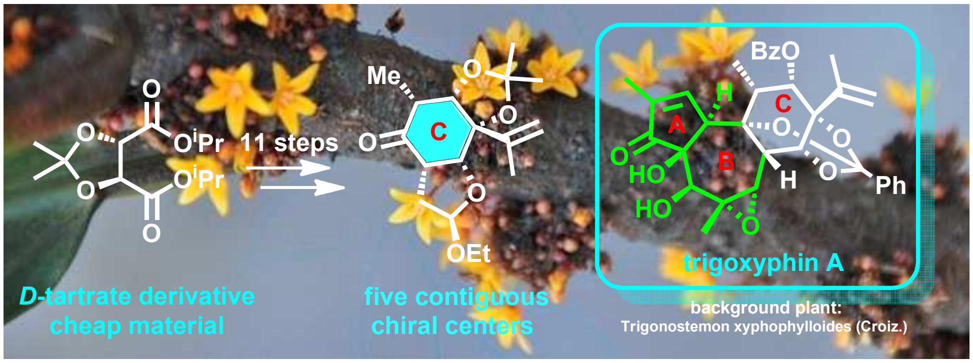
28 J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.,* 1973, **14**, 4607.

29 Comin's reagent and Tf_2O were also tested, but both resulted in lower yields. Comin's reagent condition, see: Submitted by D. L. Comins, A. Dehghani, C. J. Foti and S. P. Joseph. Checked by M. A. Cichy and A. B. Smith, III. *Org. Synth.,* 1997, **74**, 77. Tf_2O condition, see: (*a*) R. J. Hargrove and P. J. Stang, *J. Org. Chem.,* 1974, **39**, 581; (*b*) Submitted by P. J. Stang and T. E. Dueber. Checked by W. Jaeger and H. O. House, *Org. Synth*., 1974, **54**, 79.

30 E. M. Burgess, H. R. Penton and E. A. Taylor, *J. Org. Chem.,* 1973, **38**, 26.

31 PCC, another alternative oxidant in hydroboration-oxidation reaction, was also explored to simplify the synthesis, but failed. For related reference, see: E. J. Parish, S. Parish and H. Honda, *Synth. Commun.,* 1990. **20**, 3265.

View Article Online
DOI: 10.1039/C8CC04351E



Asymmetric synthesis of the fully functionalized six-membered ring of trigoxyphin A, a daphnane-type diterpenoid, has been accomplished concisely from *D*-tartrate derivative. Key elements of this synthesis involve the tandem ozonization/intramolecular HWE reaction to construct the α,β-unsaturated cyclohexenone skeleton, the radical cyclization to introduce the C8 chirality and sequential Kumada cross-coupling/hydroboration-oxidation to introduce the C11 chirality. The target substructure could be synthetically achieved in a multi-gram scale.