Tetrahedron Letters 54 (2013) 5567–5572

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total syntheses of proposed (±)-trichodermatides B and C

Qian Li [a], Yan-Shuang Xu [a], Gregory A. Ellis [b], Timothy S. Bugni [b,*], Yu Tang [a,*], Richard P. Hsung [b,*]

[a] School of Pharmaceutical Science and Technology, Key Laboratory for Modern Drug Delivery and High-Efficiency, Tianjin University, Tianjin 300072, PR China
[b] Division of Pharmaceutical Sciences, Department of Chemistry, School of Pharmacy, University of Wisconsin, Madison, WI 53705, USA

ARTICLE INFO

Article history:
Received 2 July 2013
Revised 19 July 2013
Accepted 25 July 2013
Available online 2 August 2013

Keywords:
Trichodermatides
oxa-[3+3] Annulation
Biosynthesis
Davis' oxaziridine
Electrocyclic ring-opening
DFT calculations

ABSTRACT

Total syntheses of putative (±)-trichodermatides B and C are described. These efficient syntheses feature the *oxa*-[3+3] annulation strategy, leading to B and C along with their respective C2-epimers. However, these synthetic samples are spectroscopically very different from the natural products. DFT calculations of C13 chemical shifts are conducted and the predicted values are in good agreement with those of synthetic samples, thereby questioning the accuracy of structural assignments of trichodermatides B and C.
Published by Elsevier Ltd.

In 2008, Pei and co-workers[1] reported the isolation of four new natural products, trichodermatides A–D (Fig. 1), from the marine-derived fungus *Trichoderma reesei*, which is a source of natural products known to possess a vast array of rich bioactivities.[2] While trichodermatide A signifies an unprecedented pentacyclic manifold for a polyketide and was the subject of a recent elegant total synthesis by Hiroya,[3] trichodermatide B–D are structural relatives of known polyketide metabolites such as the koninginin family found from the culture of *Trichoderma koningii*.[4,5] The key differences between trichodermatides and koninginins are the position of the hydroxyl group, and the oxidation state on the C9-side aliphatic chain.

We are interested in pursuing total syntheses of these novel natural products because of their activities against A375-S2 human melanoma cell line[1] as well as agricultural significance of this entire structural array,[4,5] and because of the potential to apply an *oxa*-[3+3] annulation strategy in these syntheses.[6,7] Our *oxa*-[3+3] annulation represents a biomimetic approach,[8,9] that has proven to be a powerful tandem strategy[10] for natural product synthesis.[11] More importantly, while authors illustrated a possible biosynthetic pathway for trichodermatide A, we envisioned an alternative biosynthetic pathway that would involve intermediates related to trichodermatide B and/or C because trichodermatide A essentially represents a union of α-hydroxy-1,3-cyclohexanedione with a derivative of trichodermatide B or C [highlighted in red]. Consequently, we first targeted syntheses of trichodermatide B and/or C, but encountered an unexpected outcome during this pursuit. That is we are unable to match them spectroscopically with the reported data.[1] We wish to communicate here this unexpected encounter.

Our general synthetic strategy for approaching trichodermatide B and C is shown in Scheme 1. Both B and C can be envisioned from the common intermediate **1**, derived from the *oxa*-[3+3] annulation of aldehyde **2** with 1,3-cyclohexanedione **3**. We recognized that while the same annulation with diketone **5** may lead to a more convergent route, lack of regioselectivity could lead to a troublesome mixture of regioisomers **4** and **4′**.[12] While perhaps more conservative, the use of 1,3-cyclohexanedione **3** would present no such regiochemical issue. It is also noteworthy that to quickly assess the feasibility of our plan, we first pursued racemic syntheses.

Enal **8** could be readily constructed in 6 steps from propargyl alcohol and heptanal (Scheme 2).[13] With enal **8** in hand, total synthesis of trichodermatide B could be accomplished. As shown in Scheme 3, L-proline promoted *oxa*-[3+3] annulation of enal **8** with 1,3-cyclohexanedione **3** was carried out in high yield.[12] Subsequent standard hydrogenation and α-hydroxylation using Davis' oxaziridine would afford alcohol **11**.[14] A sequence of standard protection, desilylation, Dess–Martin periodinane oxidation, and deacetylation would give trichodermatide B [putative—vide infra] and its C2-epimer as a 2:1 isomeric mixture.

Total synthesis of trichodermatide C took two different approaches. The most direct one would involve *oxa*-[3+3] annulation of dienal **13** (Scheme 4). Intriguingly, using either the piperidine/Ac_2O or the L-proline protocol[12] led to only the Knoevenagel condensation product **15**. It is possible that the desired annulation product **14** was initially formed, but the ring-opened form is

* Corresponding authors.
E-mail addresses: tbugni@pharmacy.wisc.edu (T.S. Bugni), yutang@tju.edu.cn (Y. Tang), rhsung@wisc.edu (R.P. Hsung).

0040-4039/$ - see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2013.07.137

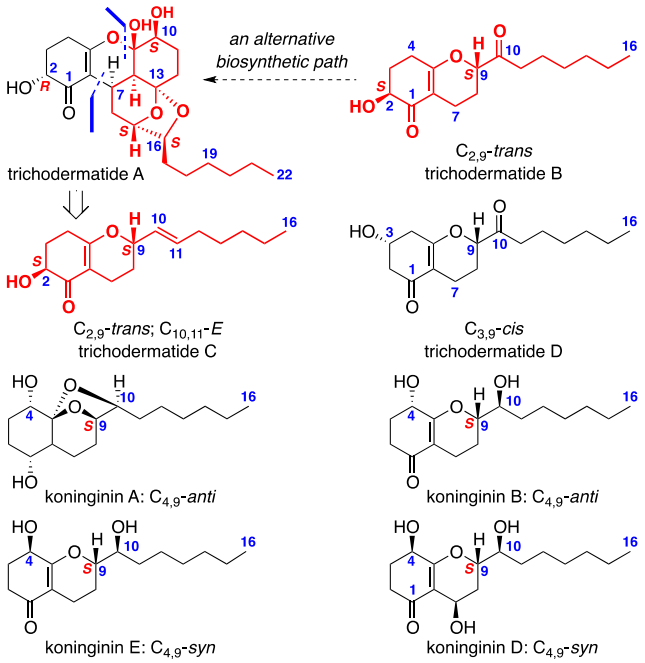
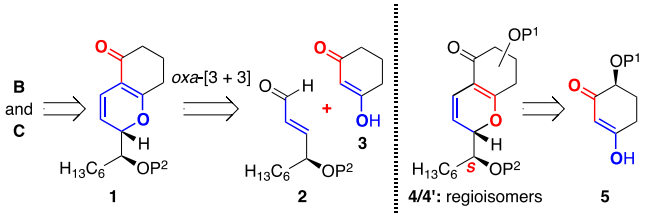


Figure 1. Trichodermatides A–D.

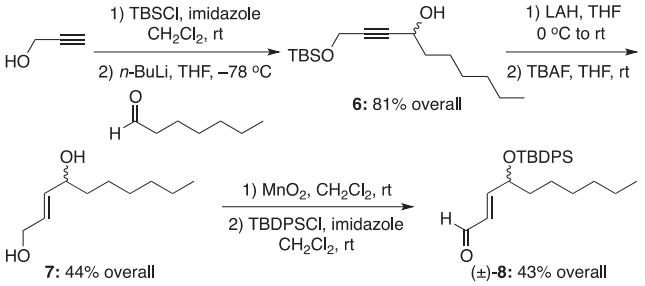


Scheme 1. General retrosynthetic strategy.

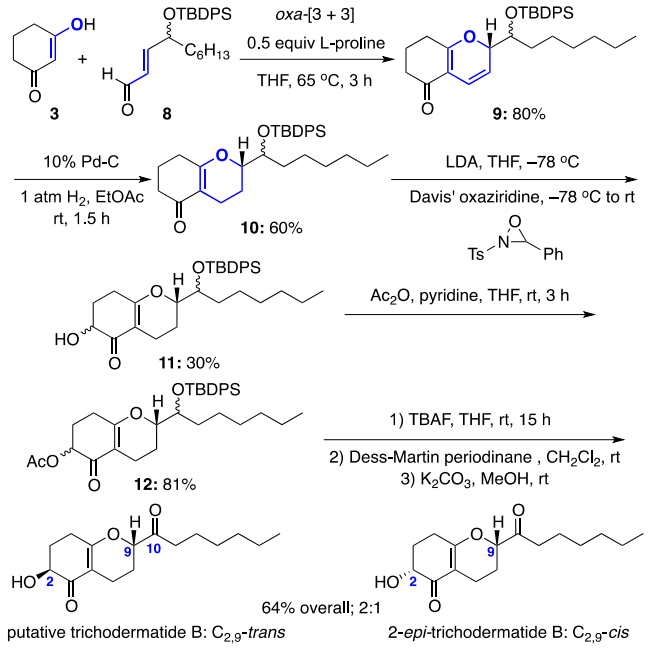
favored due to the extended conjugation. It is noteworthy that this is the first reported attempt of an *oxa*-[3+3] annulation using dienal.[6]

Ultimately, total synthesis of trichodermatide C was accomplished using the common intermediate **10** used for the synthesis of trichodermatide B via a sequence of desilylation, Martin's sulfurane promoted elimination, and α-hydroxylation via Davis' oxaziridine (Scheme 5). Again, trichodermatide C [putative—vide infra] and its C2-epimer were obtained as an inseparable isomeric mixture with a ratio of 1:1.

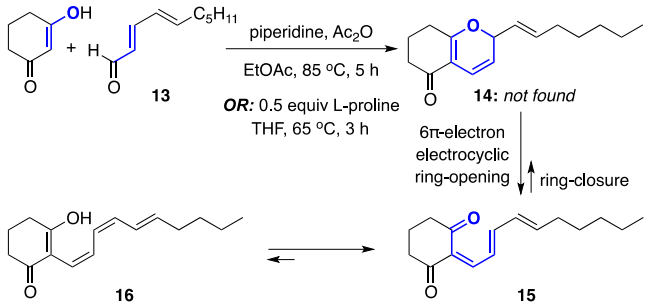
Unfortunately, neither the synthetic trichodermatide B nor C matched the reported ^{1}H and ^{13}C NMR chemical shifts for the natural products (see Figs. 2 and 3). Although we were unable to separate the C2-epimer from B [or C2-epimer from C], we could



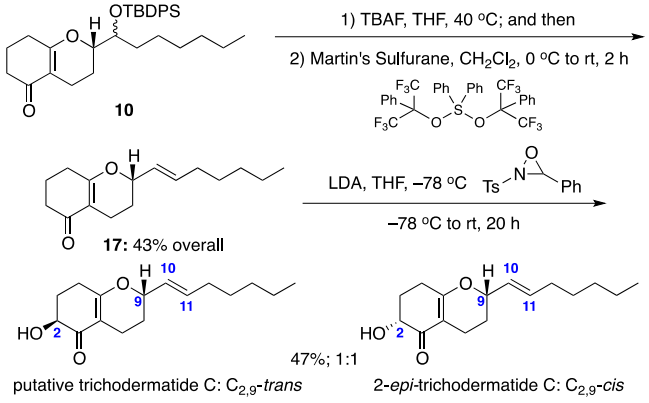
Scheme 2. Synthesis of the key enal **8**.



Scheme 3. Total syntheses of trichodermatide B and its C2-epimer.



Scheme 4. An attempt on *oxa*-[3+3] annulation using Dienal **13**.



Scheme 5. Total syntheses of trichodermatide C and its C2-epimer.

clearly distinguish key downfield proton resonances in B [or C] from its C2-epimer via COSY. In addition, in each case of B and C, there are a significant number of non-overlapping and resolved C13 resonances for the C2,9-*trans* and C2,9-*cis* diastereomers. Consequently, a seemingly undesirable stereorandom total synthesis of B [or C] turned into an opportunity that allowed us to compare both B and its C2-epimer with the corresponding natural product.

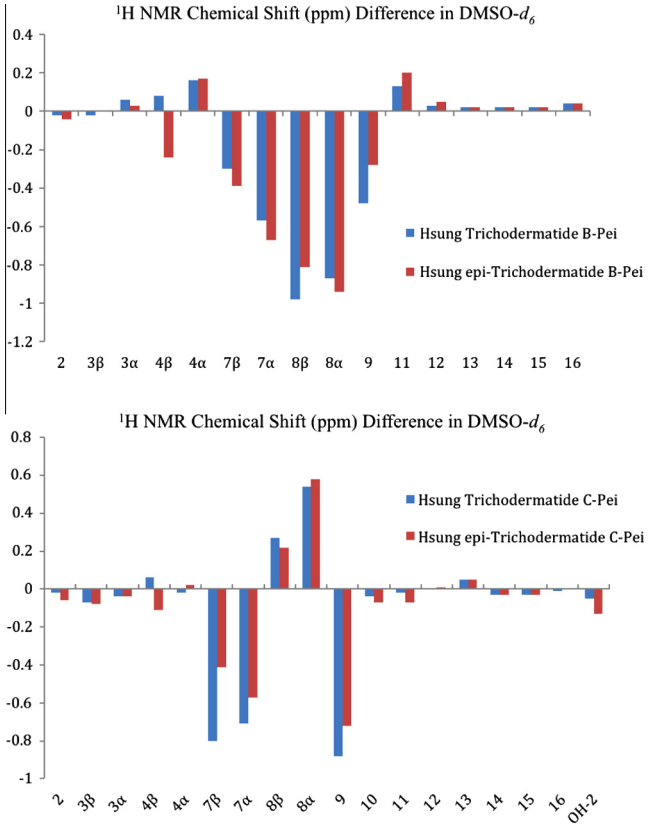


Figure 2. ¹H NMR comparison: synthetic and reported chemical shifts.

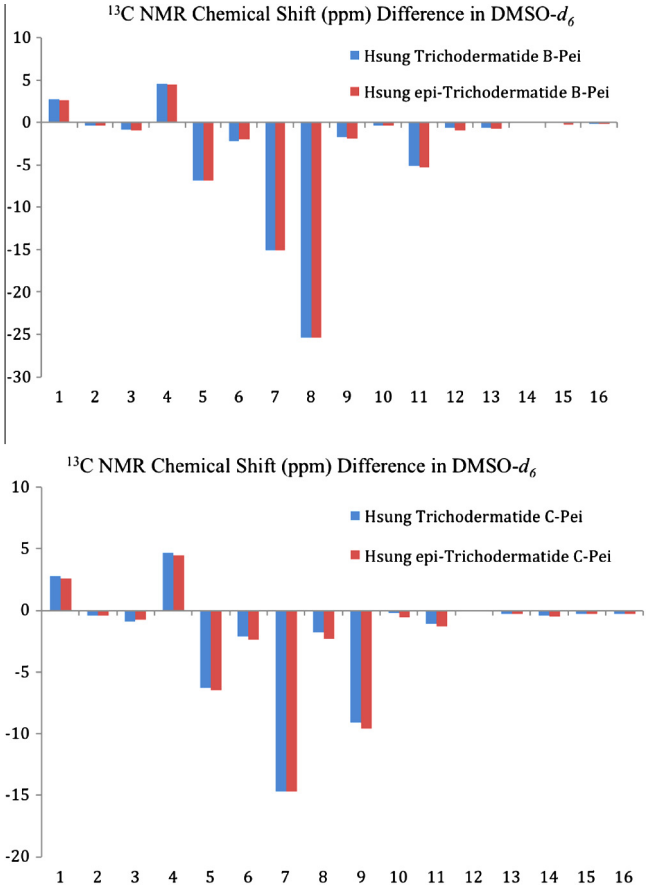


Figure 3. ¹³C NMR comparison: synthetic and reported chemical shifts.

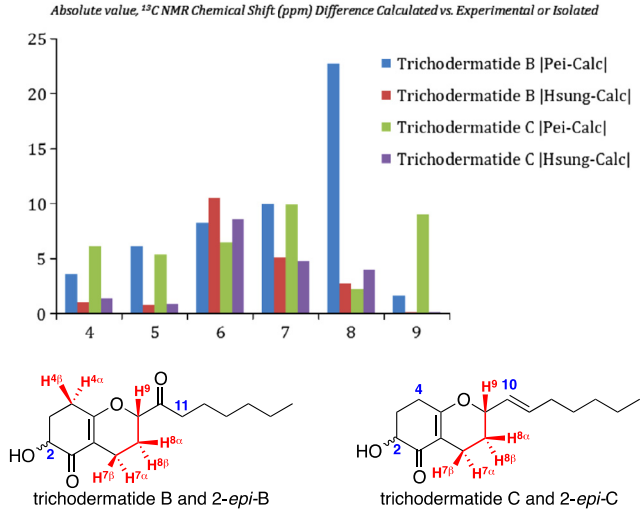


Figure 4. ¹³C NMR comparison: synthetic and DFT calculated shifts.

Our inability to match them suggests that the possible mis-assignment is not in the relative stereochemistry at C2 and C9 of the putative trichodermatide B and C.

To provide better assurance of the integrity of our syntheses, we pursued DFT calculations to predict C13 chemical shifts for the synthesized structures. For the low energy conformer of each structure,[16,17] geometry optimization and NMR calculations [B3LYP/6-31G(d,p)][18] were performed with GAUSSIAN 09.[19] The predicted values are in very good agreement with those recorded for the synthetic samples and not those for the isolated samples, thereby suggesting possible erroneous assignments in the original isolation paper (see Fig. 4 for partial listings].[15] When comparing the synthetic values with the isolated values in regard to difference from the calculated values, most of the largest deviations were in the area of C5–C9 (Fig. 4; respective C2-epimers excluded for clarity). Most importantly, for each structure, we used the DP4 probability method[20] to check which data set would most closely match the calculated values. Consequently, by using the DP4 probability method, we observed a 100.0% probability for matching the calculated values with those reported here for our synthetic samples, and a 0.0% probability for matching with those reported by Pei and co-workers.

Overall, spectroscopic comparisons between our synthetic samples and the isolated ones reveal the major differenced residue at C4 and C7–C9 for trichodermatide B and its C2-epimer, and C7–C9 for trichodermatide C and its C2-epimer. These differences imply a possible skeleton difference in the structural assignment. Attempts were made but failed to reassign the isolated structures based on available data.

We have described here total syntheses of proposed (±)-trichodermatides B and C. These total syntheses are efficient and feature the *oxa*-[3+3] annulation strategy, leading to trichodermatide B and C along with their respective C2-epimers. However, the synthetic samples are spectroscopically very different from the reported natural products. DFT calculations of C13 chemical shifts were conducted and predicted values are in good agreement with those of the synthetic samples, thereby questioning the accuracy of structural assignments of trichodermatide B and C.

Acknowledgments

Y.T. thanks Natural Science Foundation of China for generous funding [Nos. 21172169 and 21172168]. T.S.B. thanks NIH [GM104192] for generous funding. R.P.H. thanks University of

Wisconsin-Madison Vilas Associate for a faculty award. Service from The Instrumentation Center at School of Pharmaceutical Science and Technology of Tianjin University is greatly appreciated.

References and notes

1. Sun, Y.; Tian, L.; Huang, J.; Ma, H.-Y.; Zheng, Z.; Lv, A.-L.; Yasukawa, K.; Pei, Y.-H. *Org. Lett.* **2008**, *10*, 393.
2. For a review, see: (a) Bugni, T. S.; Ireland, C. M. *Nat. Prod. Rept.* **2004**, *21*, 143; (b) Garo, E.; Starks, C. M.; Jensen, P. R.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2003**, *66*, 423; (c) Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011.
3. Shigehisa, H.; Suwa, Y.; Furiya, N.; Nakaya, Y.; Fukushima, M.; Ichihashi, Y.; Hiroya, K. *Angew. Chem., Int. Ed.* **2013**, *125*, 3734.
4. For koninginn A: (a) Cutler, H. G.; Himmelsbach, D. S.; Arrendale, R. F.; Cole, P. D.; Cox, R. H.; Koninginin, A. *Agric. Biol. Chem.* **1989**, *53*, 2605; (b) Cutler, H. G.; Jacyno, J. M.; Phillips, R. S.; Von Tersch, R. L.; Cole, P. D.; Montemurro, N. *Agric. Biol. Chem.* **1991**, *55*, 243; For koninginin B: (c) Culter, H. G.; Himmelsbach, D. S.; Yagen, B.; Arrendale, R. F.; Jacyno, J. M.; Cole, P. D.; Cox, R. H. *J. Agric. Food Chem.* **1991**, *39*, 977; For koninginin E: (d) Parker, S. R.; Culter, H. G.; Schreiner, P. R. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 1747.
5. Also see—equally significant paper: (a) Dunlop, R. W.; Simon, A.; Sivasithamparam, K.; Ghisalberti, E. L. *J. Nat. Prod.* **1989**, *52*, 67; (b) Almassi, F.; Ghisalberti, E. L.; Narbey, M. J. *J. Nat. Prod.* **1991**, *54*, 396; (c) Ghisalberti, E. L.; Rowland, C. Y. *J. Nat. Prod.* **1993**, *56*, 1799.
6. For reviews, see: (a) Buchanan, G. S.; Feltenberger, J. B.; Hsung, R. P. *Curr. Org. Syn.* **2010**, *7*, 363; (b) Gademann, K.; Lawrence, A. K. *Synthesis* **2008**, 331; (c) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349; (d) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23; (e) Hsung, R. P.; Cole, K. P. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier Science, Pergamon Press: Oxford, UK, 2004; Vol. 4, p 41.
7. For recent development on *oxa*-[3+3] annulations, see: (a) Fotiadou, A. D.; Zografos, A. L. *Org. Lett.* **2012**, *14*, 5664; (b) Hu, J.; Dong, W.; Wu, X.-Y.; Tong, X. *Org. Lett.* **2012**, *14*, 5530; (c) dos Samntos, W. H.; da Silva-Filho, L. C. *Synthesis* **2012**, 3361; (d) Lee, Y. R.; Pandit, R. P. *Synthesis* **2012**, 2910; (e) Parker, K. A.; Mindt, T. L. *Tetrahedron* **2011**, *67*, 9779; (f) Jung, E. J.; Park, B. H.; Lee, Y. R. *Green Chem.* **2003**, *2010*, 12; (g) Yamamoto, Y.; Itonaga, K. *Org. Lett.* **2009**, *11*, 717; (h) Sagar, R.; Park, J.; Koh, M.; Park, S. B. *J. Org. Chem.* **2009**, *74*, 2171; (i) Hubert, C.; Moreau, J.; Batany, J.; Duboc, A.; Hurvois, J.-P.; Renaud, J.-L. *Adv. Synth. Catal.* **2008**, *350*, 40; (j) Brioche, J. C. R.; Goodenough, K. M.; Whatrup, D. J.; Harrity, J. P. A. *J. Org. Chem.* **1946**, *2008*, 73.
8. For a recent review on biomimetic synthesis, see: Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rept.* **2008**, *25*, 254.
9. Also see: see: (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730; (b) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757; (c) Pindur, U.; Schneider, G. H. *Chem. Soc. Rev.* **1994**, 409.
10. For leading reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131; (c) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47.
11. For recent applications of *oxa*-[3+3] annulations in natural product syntheses, see: (a) Song, L.; Yao, H.; Zhu, L.; Tong, R. *Org. Lett.* **2013**, *15*, 6; (b) Li, H.; Tang, Y.; Hsung, R. P. *Tetrahedron Lett.* **2012**, *53*, 6138; (c) Buchanan, G. S.; Cole, K. P.; Tang, Y.; Hsung, R. P. *J. Org. Chem.* **2011**, *76*, 7027; (d) Buchanan, G. S.; Cole, K. P.; Li, G.; Tang, Y.; You, L.; Hsung, R. P. *Tetrahedron* **2011**, *67*, 10105; (e) Yamashita, S.; Iso, K.; Kitajima, K.; Himura, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408; (f) Wang, X.; Lee, Y. R. *Tetrahedron* **2011**, *67*, 9179; (g) Hosokawa, S.; Matsushita, K.; Tokimatsu, S.; Toriumi, T.; Suzuki, Y.; Tatsuta, K. *Tetrahedron Lett.* **2010**, *51*, 5532; (h) Tang, Y.; Cole, K. P.; Buchanan, G. S.; Li, G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 1591; (i) Wang, X.; Lee, Y. R. *Tetrahedron* **2009**, *65*, 10125; (j) Jeso, V.; Nicolaou, K. C. *Tetrahedron Lett.* **2009**, *50*, 1161; (k) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem.* **2008**, *73*, 4313; (l) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413.
12. (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690; (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Wei, L.-L.; Sklenicka, H. M.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729.
13. *Alkynol* ***6***: R_f = 0.44 [10% EtOAc in petroleum ether]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.7 Hz), 1.29–1.38 (m, 6H), 1.43–1.45 (m, 2H), 1.65–1.72 (m, 2H), 4.35 (s, 2H), 4.38 (t, 1H, J = 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.1, 14.0, 18.2, 22.5, 25.0, 25.8, 28.9, 31.7, 37.7, 51.7, 62.5, 83.4, 85.9; IR (KBr) cm^{-1} 3352 br s, 2955s, 2930s, 2858s, 1680w, 1464m, 1254m, 1084m, 837s; *m*/*e* calcd for $C_{16}H_{32}O_2SiNa^+$ $(M+Na)^+$ 307.2064, found 307.2062.
To a heterogeneous suspension of LAH (6.50 g, 170.0 mmol) in THF (500 mL) was added at 0 °C a solution of alkynol **6** (32.3 g, 114.0 mmol) in THF (100 mL) via cannula. The reaction mixture was stirred at 0 °C for 5 min before it was warmed to rt and stirred for an additional 2 h. The mixture was treated sequentially with H_2O (6.5 mL) and 10% aq KOH (11 mL) in an ice bath and stirred for 10 min after quenching. After the addition of another portion of H_2O (17 mL), the mixture was filtered, and the insoluble aluminum salt was repeatedly washed with EtOAc. The combined filtrates were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude and colorless *trans*-allylic alcohol (26.7 g, 84%) was used for the next step without purification.
To a solution of the above *trans*-allylic alcohol (3.50 g, 12.2 mmol) in THF (60 mL) was added solid TBAF (3.80 g, 14.6 mmol, 1.2 equiv). The resulting mixture was stirred for 12 h at rt before it was quenched with H_2O. The aqueous layer was extracted with equal volume of EtOAc three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified using flash silica gel column chromatography (Gradient eluent: 0–50% EtOAc in petroleum ether) to afford the desired diol **7** as colorless oil (1.09 g, 52%). R_f = 0.16 [50% EtOAc in petroleum ether]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.2 Hz), 1.24–1.37 (m, 8H), 1.49–1.54 (m, 2H), 4.13 (m, 1H), 4.16 (d, 1H, J = 5.2), 5.74 (dd, 1H, J = 6.3, 15.4 Hz), 5.83 (dt, 1H, J = 5.1, 15.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 22.5, 25.3, 29.2, 31.7, 37.1, 62.7, 72.2, 129.6, 134.5; IR (KBr) cm^{-1} 3270 br s, 2921s, 2856s, 1463m, 1327m, 1083s, 1007s, 908m; mass spectrum (ESI): *m*/*e* (% relative intensity) 194.8 (100) $(M+Na)^+$.
To a solution of diol **7** (300.0 mg, 1.70 mmol) in CH_2C1_2 (20 mL) was added MnO_2 (3.80 g, 43.6 mmol) at rt. The resulting mixture was stirred for 20 h before being filtered. After filtration, the excess solvent was removed in vacuo. The crude yellow residue was purified using flash silica gel column chromatography (Gradient eluent: 10–50% EtOAc in petroleum ether) to afford the desired *trans*-enal (86.0 mg, 71%, based on recovered start material) as pale yellow oil. R_f = 0.72 [50% EtOAc in petroleum ether]; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.91 (t, 3H, J = 6.0 Hz), 1.29–1.33 (m, 6H), 1.36–1.41 (m, 2H), 1.47–1.50 (m, 1H), 1.53–1.57 (m, 1H), 4.29–4.30 (m, 1H), 5.19 (br s, 1H), 6.20 (dd, 1H, J = 8.0, 15.4 Hz), 7.07 (dd, 1H, J = 4.2, 15.4 Hz), 9.58 (d, 1H, J = 8.0 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 13.8, 22.0, 24.7, 28.6, 31.2, 35.9, 69.2 (d), 129.5 (d), 162.2, 194.2 (d); IR (KBr) cm^{-1} 3456 br s, 2929s, 2857s, 2732w, 1690s, 1642m, 1466m, 1126w; mass spectrum (ESI): *m*/*e* (% relative intensity) 171.0 (100) $(M+H)^+$; *m*/*e* calcd for $C_{10}H_{18}O_2Na^+$ $(M+Na)^+$ 193.1199, found 193.1199.
To a solution of the above *trans*-enal (400.0 mg, 2.35 mmol) in CH_2Cl_2 (15 mL) were added imidazole (320 mg, 4.7 mmol) and TBDPSCl (0.79 mL, 3.0 mmol) at 0 °C. After stirring at rt for 6 h, the reaction mixture was quenched with H_2O and the mixture was concentrated under reduced pressure. The aqueous fraction was extracted with equal volume of CH_2Cl_2 three times. The combined organic phases were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Gradient eluent: 0–10% EtOAc in petroleum ether) to provide the desired enal **8** (0.58 g) in 61% yield. R_f = 0.76 [20% EtOAc in petroleum ether]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84 (t, 3H, J = 7.3 Hz), 1.08 (s, 9H), 1.13–1.15 (m, 5H), 1.20–1.24 (m, 2H), 1.25–1.28 (m, 1H), 1.45–1.55 (m, 2H), 4.44–4.47 (m, 1H), 6.15 (ddd, 1H, J = 1.4, 8.0, 15.6 Hz), 6.68 (dd, 1H, J = 5.2, 15.6 Hz), 7.33–7.44 (m, 6H), 7.60 (dd, 2H, J = 1.3, 8.0 Hz), 7.66 (dd, 2H, J = 1.3, 8.0 Hz), 9.45 (d, 1H, J = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 19.3, 22.5, 24.0, 27.0, 29.1, 31.5, 36.7, 72.5, 127.6, 129.9, 130.9, 133.5 (d), 135.8 (d), 159.2, 193.5; IR (KBr) cm^{-1} 3736s, 2933m, 2340w, 1697m, 1518m, 692s; *m*/*e* calcd for $C_{26}H_{37}O_2Si^+$ $(M+H)^+$ 409.2557, found 409.2554.
To a solution of enal **8** (325.0 mg, 0.80 mmol) in THF (8 mL) were added L-proline (46.0 mg, 0.40 mmol) and 1,3-cyclohexanedione (98.0 mg, 0.87 mmol). The vessel was sealed under nitrogen and placed in a 65 °C oil bath for 3 h. After TLC analysis indicated complete consumption of the starting materials, the excess solvent was removed in vacuo. The crude residue was purified using flash silica gel column chromatography (Gradient eluent: 0–20% EtOAc in petroleum ether) to afford the desired *oxa*-[3+3] annulation product **9** (324.0 mg, 80%) as colorless oil. Characterized as an inseparable mixture of two diastereomers: R_f = 0.50 [20% EtOAc in petroleum ether]; ^{1}H NMR (600 MHz, $CDCl_3$) diastereomer-I: δ 0.83 (t, 3H, J = 7.1 Hz), 1.03 (s, 9H), 1.05–1.14 (m, 7H), 1.40–1.46 (m, 1H), 1.52–1.58 (m, 1H), 1.98–2.04 (m, 1H), 1.77–1.91 (m, 3H), 2.22–2.36 (m, 3H), 3.81–3.85 (m, 1H), 4.81 (dd, 1H, J = 2.4, 4.9 Hz), 5.30 (dd, 1H, J = 2.4, 10.2 Hz), 6.53 (dd, 1H, J = 2.0, 10.2 Hz), 7.29–7.44 (m, 6H), 7.64–7.70 (m, 4H); resolved proton resonances for diastereomer-II: δ 1.17–1.22 (m, 7H), 2.09–2.15 (m, 1H), 4.91 (m, 1H), 5.33 (dd, 1H, J = 3.1, 10.2 Hz), 6.50 (dd, 1H, J = 1.3, 10.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) diastereomer-I: δ 14.0, 19.47, 20.4, 22.5, 25.4, 27.0, 27.9, 29.1, 31.6, 32.43, 36.3, 74.9, 80.7, 111.2, 114.1, 119.1, 127.5, 129.7, 133.9, 135.9, 172.7, 194.7; non-overlapping carbon resonances for diastereomer-II: 19.49, 20.5, 24.8, 26.9, 28.0, 29.2, 32.40, 74.6, 79.5, 111.5, 114.9, 118.6, 127.2, 129.3, 133.5, 136.1, 172.5; IR (KBr) cm^{-1} 3427w, 2934s, 2859m, 1723m, 1614m, 1420s, 1107s, 818w, 702s; mass spectrum (ESI): *m*/*e* (% relative intensity) 503.2 (100) $(M+H)^+$; *m*/*e* calcd for $C_{32}H_{42}O_3SiNa^+$ $(M+Na)^+$ 525.2795, found 525.2815.
To a solution of **9** (0.32 g, 0.64 mmol) in EtOAc (6 mL) was added 5% Pd–C (0.14 g, 0.064 mmol, 0.10 equiv). The resulting mixture was stirred under an atmosphere of H_2 (balloon) at rt for 1.5 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified using flash silica gel column chromatography (Gradient eluent: 0–20% EtOAc in petroleum ether) to afford **10** as colorless oil (191.0 mg, 60%). Characterized as an inseparable mixture of two diastereomers: R_f = 0.48 [20% EtOAc in petroleum ether]; ^{1}H NMR (600 MHz, $CDCl_3$) diastereomer-I: δ 0.82 (t, 3H, J = 7.1 Hz), 1.05 (s, 9H), 1.06–1.11 (m, 3H), 1.11–1.23 (m, 4H), 1.24–1.29 (m, 1H), 1.35–1.41 (m, 1H), 1.48–1.54 (m, 1H), 1.80–1.89 (m, 3H), 1.90–1.94 (m, 1H), 1.95–2.06 (m, 2H), 2.19–2.24 (m, 1H), 2.27–2.35 (m, 2H), 2.47–2.50 (m, 1H), 3.77 (dt, 1H, J = 2.4, 10.9 Hz), 3.91 (td, 1H, J = 2.7, 6.2 Hz), 7.32–7.44 (m, 6H), 7.64–7.71 (m, 4H); resolved proton resonances for diastereomer-II: δ 0.84 (t, 3H, J = 7.1 Hz), 1.42–1.47 (m, 1H), 2.11–2.16 (m, 1H), 2.37–2.41 (m, 1H), 3.82 (dd, 1H, J = 5.8, 10.7 Hz), 3.86 (ddd, 1H, J = 1.8, 5.4, 10.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) diastereomer-I: δ 14.0, 17.6, 19.5, 20.2, 20.89, 22.4, 25.3, 27.0, 28.4, 29.1, 31.5, 33.2, 36.6, 74.1, 80.0, 111.50, 127.5, 129.6, 134.1, 136.1, 171.7, 198.1; non-overlapping carbon resonances for diastereomer-II: δ 17.8, 20.85, 22.5, 24.7, 28.2, 29.3, 31.6, 36.6, 74.3, 79.9, 111.55, 127.3, 129.4, 133.9,

135.9; IR (KBr) cm^{-1} 2953s, 2931s, 2857s, 1655m, 1625s, 1397m, 1110s, 738m, 703s; mass spectrum (ESI): *m/e* (% relative intensity) 505.2 (100) $(M+H)^+$; *m/e* calcd for $C_{32}H_{44}O_3SiNa^+$ $(M+Na)^+$ 527.2952, found 527.2959.

A 1.0 M solution of LDA was prepared from a solution of di-isopropyl amine (1.40 mL) in THF (5.60 mL) and *n*-butyl lithium (2.0 mL, 2.4 M in hexanes) at −78 °C. To a solution of **10** (676.0 mg, 1.34 mmol) in THF (13 mL) was added the above LDA solution (2.70 mL, 2.70 mmol) at −78 °C. The resulting enolate solution was stirred at −78 °C for 30 min before the addition of a solution of Davis' oxaziridine (614.0 mg, 2.0 mmol) in THF (5 mL). The reaction mixture was then stirred for an additional 30 min at −78 °C before it was warmed up to rt and stirred for an additional 18 h. The reaction mixture was quenched with sat aq NH_4Cl (25 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash silica gel column chromatography (Gradient eluent: 0–20% EtOAc in petroleum ether) to give alcohol **11** as yellow oil (211.0 mg, 30%). R_f = 0.22 [30% EtOAc in petroleum ether]; mass spectrum (ESI): *m/e* (% relative intensity) 521.5 (100) $(M+H)^+$; *m/e* calcd for $C_{32}H_{44}O_4SiNa^+$ $(M+Na)^+$ 543.2901, found 543.2919.

To a solution of the above alcohol **11** (25.0 mg, 0.048 mmol) in pyridine (1 mL) was added Ac_2O (49.8 μL, 0.48 mmol, 10.0 equiv). The resulting mixture was stirred at rt for 3 h before pyridine was removed in vacuo. The yellow crude residue was purified using flash silica gel column chromatography (Gradient eluent: 0–20% EtOAc in petroleum ether) to give acetate **12** as yellow oil (22.0 mg, 81% yield).

To a solution of the above acetate **12** (22.0 mg, 0.39 mmol) in THF (1 mL) was added TBAF (0.060 mL, 1.0 M in THF, 0.059 mmol) at 0 °C. The reaction mixture was stirred at rt for 1.5 h before sat aq NH_4Cl solution was then added and the aqueous phase was extracted three times with equal volume of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude residue was achieved using flash silica gel column chromatography (Gradient eluent: 0–50 % EtOAc in petroleum ether) to afford the desilylated product (9.0 mg, 78%) as yellow oil. R_f = 0.23 [50% EtOAc in petroleum ether]; mass spectrum (ESI): *m/e* (% relative intensity) 325.5 (100) $(M+H)^+$; *m/e* calcd for $C_{18}H_{28}O_5Na^+$ $(M+Na)^+$ 347.1829, found 347.1837.

To a stirring solution of the above desilylated product (12.0 mg, 0.040 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (33.0 mg, 0.077 mmol) at 0 °C. The resulting mixture was stirred at rt for 2 h before it was quenched with sat aq $Na_2S_2O_3/NaHCO_3$ (7/1) (1 mL). The quenched mixture was stirred vigorously until there were two distinct layers. The crude product was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (Gradient eluent: 0–10% EtOAc in petroleum ether) to afford the desired ketone intermediate (11.0 mg, 92%) as colorless oil. Characterized as an inseparable mixture of two diastereomers: R_f = 0.76 [50% EtOAc in petroleum ether]; ^1H NMR (600 MHz, $CDCl_3$) diastereomer-I: δ 0.88 (t, 3H, *J* = 6.5 Hz), 1.27–1.34 (m, 6H), 1.57–1.61 (m, 2H), 1.74–1.81 (m, 1H), 1.98–2.03 (m, 1H), 2.04–2.14 (m, 2H), 2.17 (s, 3H), 2.23–2.27 (m, 1H), 2.34–2.39 (m, 2H), 2.49–2.66 (m, 2H), 2.72–2.75 (m, 1H), 4.57 (dd, 1H, *J* = 4.1, 6.3 Hz), 5.32 (t, 1H, *J* = 4.7 Hz); resolved proton resonances for diastereomer-II: δ 2.41–2.47 (m, 2H), 4.38 (dd, 1H, *J* = 4.5, 9.4 Hz), 5.30 (t, 1H, *J* = 4.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) diastereomer-I: δ 14.0, 15.9, 17.0, 20.9, 22.4, 23.0, 26.5, 26.9, 28.8, 31.5, 38.1, 72.2, 80.9, 110.5, 168.9, 170.3, 191.8, 207.4; non-overlapping carbon resonances for diastereomer-II: δ 22.5, 22.9, 26.3, 27.0, 38.2, 81.1, 110.8, 168.8; IR (KBr) cm^{-1} 3687m, 2920s, 2855m, 1732m, 1620w, 1457w; mass spectrum (ESI): *m/e* (% relative intensity) 345.5 (100) $(M+Na)^+$; *m/e* calcd for $C_{18}H_{26}O_5Na^+$ $(M+Na)^+$ 345.1672, found 345.1682.

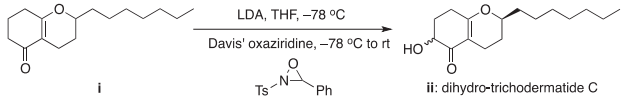
To a solution of the above ketone (9.00 mg, 0.028 mmol) in MeOH (0.5 mL) was added K_2CO_3 (7.70 mg, 0.056 mmol, 2.0 equiv) at rt. The reaction mixture was vigorously stirred for 2 h as the solution turned yellow. The mixture was then diluted with EtOAc (10 mL) and washed with aq NaOH (5 mL, 0.1 M). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash silica gel column chromatography (Gradient eluent: 0–10% EtOAc in petroleum ether) to give trichodermatide B and its C2-epimer as yellow needles (7.0 mg, 90%). Characterized as an inseparable mixture of two diastereomers: R_f = 0.38 [50% EtOAc in petroleum ether]; ^1H NMR (600 MHz, DMSO-d_6) putative B: δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.24–1.32 (m, 6H), 1.46–1.54 (m, 2H), 1.72–1.85 (m, 2H), 2.02–2.16 (m, 3H), 2.22–2.25 (m, 1H), 2.42–2.55 (m, 3H), 2.57–2.67 (m, 1H), 3.92 (dd, 1H, *J* = 4.9, 12.3 Hz), 4.66 (dd, 1H, *J* = 3.1, 8.2 Hz); resolved proton resonances for the putative 2-*epi*-B: δ 1.95–2.00 (m, 1H), 3.90 (dd, 1H, *J* = 5.0, 14.0 Hz), 4.86 (t, 1H, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) putative B: δ 13.8, 16.2, 21.9, 22.2, 22.53, 26.5, 28.1, 29.2, 31.0, 37.2, 70.3, 80.0, 108.5, 169.20, 197.4, 207.3; non-overlapping carbon resonances for the putative 2-*epi*-B: δ 21.7, 22.58, 26.4, 28.0, 29.1, 37.0, 79.8, 108.7, 169.24, 197.3; IR (KBr) cm^{-1} 3462m, 2931s, 2860m, 1722m, 1620s, 1388m, 1284w, 1080m; mass spectrum (ESI): *m/e* (% relative intensity) 303.6 (100) $(M+Na)^+$; *m/e* calcd for $C_{16}H_{24}O_3Na^+$ $(M+Na)^+$ 303.1566, found 303.1569.

To a solution of **10** (94.0 mg, 0.185 mmol) in THF (2 mL) was added TBAF (0.24 mL, 1.0 M in THF) dropwise at 0 °C. The resulting mixture was stirred for 5 h. The reaction was quenched with H_2O at rt and the aqueous layer was extracted with EtOAc three times in equal volume. The combined organic layers were dried over Na_2SO_4 and filtered. The crude residue was purified using flash silica gel column chromatography (Gradient eluent: 20–50% EtOAc in petroleum ether) to afford the desilylated product as colorless oil (44.0 mg, 89%). Characterized as an inseparable mixture of two diastereomers: R_f = 0.15 [30% EtOAc in petroleum ether]; ^1H NMR (600 MHz, $CDCl_3$) diastereomer-I: δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.30–1.41 (m, 6H), 1.49–1.58 (m, 3H), 1.63–1.70 (m, 1H), 1.91–2.00 (m, 3H), 2.05–2.13 (m, 2H), 2.34–2.41 (m, 4H), 2.44–2.50 (m, 1H), 3.61–3.64 (m, 1H), 3.78 (ddd, 1H, *J* = 2.2, 5.5, 10.9 Hz); resolved proton resonances for diastereomer-II: δ 3.82–3.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) diastereomer-I: δ 14.0, 17.6, 20.82, 22.5, 23.0, 25.3, 28.56, 29.2, 31.7, 32.7, 36.6, 73.0, 80.3, 111.7, 171.0, 198.1; non-overlapping carbon resonances for diastereomer-II: δ 17.5, 20.84, 25.7, 28.59, 32.1, 72.3, 80.4, 111.9, 171.3; IR (KBr) cm^{-1} 3413br s, 2931s, 2860s, 1612s, 1397s, 1080m; mass spectrum (ESI): *m/e* (% relative intensity) 267.0 (100) $(M+H)^+$; *m/e* calcd for $C_{16}H_{26}O_3Na^+$ $(M+Na)^+$ 289.1774, found 289.1770.

To a stirring solution of the above desilylated product (98.0 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was added slowly dropwise a solution of Martin's sulfurane (0.50 g, 0.74 mmol) in CH_2Cl_2 (2 mL) at rt. The resulting pale yellow solution was stirred for 2 h. After which, the excess solvent was removed in vacuo to yield a crude pale yellow oil. Purification of the crude product using flash silica gel column chromatography (Gradient eluent: 0–20% EtOAc in petroleum ether) furnished alkene **17** as colorless oil (41.0 mg, 48%). R_f = 0.52 [30% EtOAc in petroleum ether]; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.1 Hz), 1.25–1.31 (m, 4H), 1.37–1.41 (m, 2H), 1.62–1.68 (m, 1H), 1.91–1.99 (m, 3H), 2.03–2.08 (m, 2H), 2.14–2.19 (m, 1H), 2.35–2.40 (m, 5H), 4.38 (td, 1H, *J* = 2.1, 8.0 Hz), 5.52 (dd, 1H, *J* = 6.9, 15.4 Hz), 5.76 (dt, 1H, *J* = 6.7, 15.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 17.2, 20.9, 22.4, 27.2, 28.6, 28.8, 31.3, 32.2, 36.6, 77.9, 111.3, 128.0, 134.6, 171.2, 198.2; IR (KBr) cm^{-1} 3735w, 3616w, 2928s, 2859m, 2317w, 1619s, 1391m, 1179w; mass spectrum (ESI): *m/e* (% relative intensity) 249.1 (100) $(M+H)^+$; *m/e* calcd for $C_{16}H_{24}O_2Na^+$ $(M+Na)^+$ 271.1669, found 271.1668.

To a solution of alkene **17** (40.0 mg, 0.16 mmol) in THF (2 mL) at −78 °C were added TMEDA (6.00 μL) and a solution of LDA (0.32 mL, 0.32 mmol) prepared as previously described. The solution was stirred at −78 °C for 20 min before adding a solution of Davis' oxaziridine (79.0 mg, 0.32 mmol) in THF (2 mL). The reaction mixture was then stirred for an additional 5 min at −78 °C before it was warmed up to rt and stirred for an additional 20 h. The reaction mixture was quenched with sat aq NH_4Cl (5 mL), and the quenched mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected to flash silica gel column chromatography (Gradient eluent: 0–10% EtOAc in petroleum ether) to give putative trichodermatide C and it C2-epimer as colorless oil (20.0 mg, 47%). Characterized as an inseparable mixture of two diastereomers: R_f = 0.40 [30% EtOAc in petroleum ether]; ^1H NMR (600 MHz, DMSO-d_6) putative C: δ 0.85 (t, 3H, *J* = 7.2 Hz), 1.20–1.30 (m, 4H), 1.31–1.37 (m, 2H), 1.57–1.60 (m, 1H), 1.61–1.67 (m, 1H), 1.70–1.75 (m, 1H), 1.83–1.88 (m, 1H), 1.99–2.05 (m, 2H), 2.06–2.10 (m, 1H), 2.11–2.16 (m, 1H), 2.49–2.51 (m, 2H), 3.91 (ddd, 1H, *J* = 3.7, 4.9, 12.3 Hz), 4.41 (t, 1H, *J* = 7.5 Hz), 5.54 (dd, 1H, *J* = 6.7, 15.4 Hz), 5.76 (dt, 1H, *J* = 6.6, 15.4 Hz); resolved proton resonances for the putative 2-*epi*-C: δ 0.86 (t, 3H, *J* = 6.9 Hz), 1.52–1.57 (m, 1H), 1.69–1.73 (m, 1H), 1.89–1.92 (m, 1H), 2.25–2.28 (m, 1H), 2.33–2.36 (m, 1H), 2.53–2.56 (m, 1H), 3.87 (dt, 1H, *J* = 4.6, 11.3 Hz), 4.57 (td, 1H, *J* = 2.8, 6.9 Hz), 5.51 (dd, 1H, *J* = 6.9, 15.6 Hz), 5.71 (dt, 1H, *J* = 6.6, 15.4 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) putative C: δ 13.8, 17.1, 21.8, 26.4, 26.7, 28.0, 29.2, 30.7, 31.47, 70.36, 77.1, 108.4, 128.4, 133.5, 170.0, 197.4; non-overlapping carbon resonances for the putative 2-*epi*-C: δ 25.9, 26.5, 29.3, 30.6, 31.43, 70.31, 76.6, 108.1, 128.0, 133.3, 169.8, 197.2; IR (KBr) cm^{-1} 3461w, 2928s, 2860m, 1654w, 1614s, 1381m, 1190m, 1075w, 974m; mass spectrum (ESI): *m/e* (% relative intensity) 265.1 (100) $(M+H)^+$; *m/e* calcd for $C_{16}H_{24}O_3Na^+$ $(M+Na)^+$ 287.1618, found 287.1612.

14. We initially carried out a dihydro-trichodermatide C synthesis to test the use Davis' oxaziridine for alpha-hydroxylation.



i ii: dihydro-trichodermatide C

15. Personal communication was made to the corresponding author, Professor Yue-Hu Pei [http://peiyueh@vip.163.com], at School of Traditional Chinese Material Medica, Shenyang Pharmaceutical University, Shenyang 110016, PR China. However, there were no original spectra provided; and more importantly, there were no clear explanations for what appeared to be mis-assignments and/or mis-recordings. For examples:
For trichodermatide B: (i) In Table 2 on Page 4 of authors' *Organic Letters* Supplementary data, H9 is listed as 5.14 ppm (dd, *J* = 9.3 and 4.5 Hz), but on Page 11 of the same Supplementary data, ^1H NMR spectrum of trichodermatide B shows a multiplet—or a resonance that is much more complicated than 'dd' at 5.14 ppm; (ii) 3.94 ppm for H2 listed as 'ddd,' but spectrum also shows a more complicated multiplet.
For trichodermatide C: (i) In Table 2, H9 is listed as 5.29 ppm (ddd, *J* = 9.5, 7.6 and 4.5 Hz), but on Page 16, in the ^1H NMR spectrum of trichodermatide C, the resonance at ~5.29 ppm is not a 'ddd.' This is similarly true with H2, although the resolution of PDF files here is not as distinct as for trichodermatide B. (ii) H8 is now listed as 1.32 ppm—but H8 for C should be similar as in B and D ~2.80–3.00 ppm.

16. Molecular Modeling Calculations. Molecular modeling calculations were performed on a Dell Precision T5500 Linux workstation with a Xeon processor (3.3 GHz, 6-core). Low energy conformers were obtained using SPARTAN 10 software (MMFF, 10,000 conformers examined). The low energy conformer for each compound was analyzed using GAUSSIAN 09 for geometry optimization and NMR calculations (B3LYP/6-31G(d,p)). NMR shifts were referenced to TMS and benzene using the multi-standard (MSTD) approach.[21] Molecules were modeled in the gas phase.
17. Deppmeier, B. J.; Driessen, A. J.; Hehre, T. S.; Hehre, W. J.; Johnson, J. A.; Klunzinger, P. E.; Leonard, J. M.; Ohlinger, W. S.; Pham, I. N.; Pietro, W. J.; Yu, J. SPARTAN *10, v. 1.0.2.*; Wavefunction Inc.: Irvine, CA, 2011.
18. Stappen, I.; Buchbauer, G.; Robien, W.; Wolschann, P. *Magn. Reson. Chem.* **2009**, *47*, 720.
19. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T., ; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. GAUSSIAN *09, Revision A.1*; Gaussian, Inc.: Wallingford CT, 2009.
20. Smith, S. G.; Goodman, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12946.
21. Sarow, A. M.; Pellegrinet, S. C. *J. Org. Chem.* **2009**, *74*, 7254.