Enantioselective Total Synthesis of (−)-Triptolide, (−)-Triptonide, (+)-Triptophenolide, and (+)-Triptoquinonide

Dan Yang,* Xiang-Yang Ye, and Ming Xu

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

Received December 23, 1999

The first enantioselective total synthesis of (−)-triptolide (**1**), (−)-triptonide (**2**), (+)-triptophenolide (**3**), and (+)-triptoquinonide (**4**) was completed. The key step involves lanthanide triflate-catalyzed oxidative radical cyclization of (+)-8-phenylmenthyl ester **30** mediated by $Mn(OAc)_3$, providing intermediate **31** with good chemical yield (77%) and excellent diastereoselectivity (dr 38:1). (+)-Triptophenolide methyl ether (**5**) was then prepared in >99% enantiomeric excess (>99% ee), and readily converted to natural products **1**−**4**. In addition, transition state models were proposed to explain the opposite chiral induction observed in the oxidative radical cyclization reactions of chiral β-keto esters **17** (without an α-substituent) and **17a** (with an α-chloro substituent).

Introduction

Tripterygium wilfordii Hook F (TWHf), also called Lei Gong Teng (Thunder God Vine) due to its highly toxic nature, is a vinelike plant cultivated in many parts of southern China.[1] The crude extracts and refined extracts (so-called multiglycoside extracts) of TWHf have been increasingly used to treat disorders such as rheumatoid arthritis and systemic lupus erythematosus.[2] Many natural products have been isolated from TWHf (e.g., **1**−**4**),[3] and some of them show significant biological activities. For example, (−)-triptolide (**1**)[3a] and (−)-triptonide (**2**)[3a] (Figure 1) have potent antitumor,[4a,b] antiinflammatory,[4c,d] immunosuppressive,[4d−g] and antifertile activities,[4d,h] whereas (+)-triptophenolide (**3**)[3b] only shows antiinflammatory activity. Thus a great deal of efforts were made by Berchtold[5a−d] and by van Tamelen[5e−g] on the total synthesis of triptolide and its related compounds.[5h,i] We also reported a concise total synthesis of (±)-triptolide.[6] However, a more challenging task is the asymmetric synthesis of triptolide. In 1980, van Tamelen completed a synthesis of (−)-triptolide from (*l*)-dehydroabietic acid.[5g] By developing a lanthanide triflate-catalyzed asymmetric radical cyclization method,[7] we recently completed the first enantioselective total synthesis of (−)-triptolide (**1**), (−)-triptonide (**2**), (+)-triptophenolide (**3**), and (+)-triptoquinonide (**4**).[3c−e]. The results are reported in this paper.

Results and Discussion

Our retrosynthetic route for compounds **1**−**4** is depicted in Scheme 1. The key steps include (i) triepoxide construction from triptophenolide methyl ether (**5**),[8] (ii) lactone formation from tricyclic compound **A**, (iii) asymmetric radical cyclization of **B**, and (iv) construction of acyclic precursor **B**.

1. Synthesis of Acyclic Precursor 15. We started with commercially available 2-isopropyl phenol (**6a**) and used MOMCl to protect the phenol hydroxyl group (Scheme 2).[9] The resulting MOM ether **6b** was treated with *n*-BuLi,[10] and then cooled to −78 °C and quenched with iodomethane, providing compound **9** in 98% isolated yield. Compound **9** was further lithiated with *s*-BuLi/THF and quenched with 3,3-dimethylallyl bromide to give

(1) (a) *Zhong Yao Da Ci Dian*; Jiangsu Xin Yi Xue Yuan, Ed.; Shanghai Ke Xue Ji Shu Chu Ban She: Shanghai, 1994; p 2469. (b) *Shen Nong Ben Cao Jing*; Huang, S., Ed.; Zhong Yi Gu Ji Chu Ban She: Beijing, 1987.

(2) (a) Zheng, J.-R.; Xu, L.-F.; Ma, L. *J. Tradit. Chin. Med.* **1982**, *23*, 714. (b) Tao, X.; Davis, L. S.; Lipsky, P. E. *Arthritis Rheum.* **1991**, *34*, 1274. (c) Lipsky, P. E.; Tao, X.-L.; Cai, J.; Kovacs, W. J.; Olsen, N. J. U.S. Patent 5846742, 1998. (d) Li, J. *Yao Xue Tong Bao* **1985**, *20*, 101. (e) Tao, X.-L.; Sun, Y.; Dong, Y.; Shi, Y.; Xiao, Y.-L.; Di, H.; Chang, N.-C. *Chin. J. Med.* **1987**, *26*, 399. (f) Xu, W.; Zheng, J.; Lu, X. *Int. J. Dermatol.* **1985**, *24*, 152. (g) Zheng, J.; Xu, L.; Ma, L.; Wang, D.; Gao, J. *Zhongguo Yixue Kexueyuan Xuebao* **1983**, *5*, 1.

(3) (a) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194. (b) Deng, F.-X.; Zhou, B.-N.; Song, G.-Q.; Hu, C.-Q. *Acta Pharm. Sin.* **1982**, *17*, 146. (c) Morota, T.; Qin, W.-Z.; Takagi, K.; Xu, L.-H.; Maruno, M.; Yang, B.-H. *Phytochemistry* **1995**, *40*, 865. (d) Milanova, R.; Han, K.; Moore, M. *J. Nat. Prod.* **1995**, *58*, 68. (e) Milanova, R.; Stoynov, N.; Moore, M. *Enzyme Microb. Technol.* **1996**, *19*, 86.

(4) (a) Kupchan, S. M.; Schubert, R. M. *Science* **1974**, *185*, 791. (b) Lee, K. Y.; Chang, W.-T.; Qiu, D.-M.; Kao, P. N.; Rosen, G. D. *J. Biol. Chem.* **1999**, *274*, 13451. (c) Zheng, Y.-L.; Lin, J.-F.; Lin, C.-C.; Xu, Y. *Acta Pharm. Sin.* **1994**, *15*, 540. (d) Zheng, J.-R.; Gu, K.-X.; Xu, L. F.; Gao, J.-W.; Yu, Y.-H.; Tang, M.-Y. *Acta Acad. Med. Sin.* **1991**, *13*, 391. (e) Gu, W.-Z.; Chen, R.; Brandwein, S.; McAlpine, J.; Burres, N. *Int. J. Immunopharmacol.* **1995**, *17*, 351. (f) Yang, S.-X.; Gao, H.-L.; Xie, S.-S.; Zhang, W.-R.; Long, Z.-Z. *Int. J. Immunopharmacol.* **1992**, *14*, 963. (g) Qiu, D.-M.; Zhao, G.-H.; Aoki, Y.; Shi, L.-F.; Uyei, A.; Nazarian, S.; Ng, J. C.-H.; Kao, P. N. *J. Biol. Chem.* **1999**, *274*, 13443. (h) Zhen, Q.-S.; Ye, X.; Wei, Z.-J. *Contraception* **1995**, *51*, 121.

(5) (a) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977**, *42*, 2569. (b) Buckanin, R. S.; Chen, S. J.; Frieze, D. M.; Sher, F. T.; Berchtold, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 1200. (c) Frieze, D. M.; Berchtold, G. A.; Blount, J. F. *Tetrahedron Lett.* **1978**, *47*, 4607. (d) Lai, C. K.; Buckanin, R. S.; Chen, S. J.; Zimmerman, D. F.; Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1982**, *47*, 2364. (e) Garver, L. C.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 867. (f) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 1785. (g) van Tamelen, E. E.; Demers, J. P.; Taylor, E. G.; Koller, K. *J. Am. Chem. Soc.* **1980**, *102*, 5424. (h) Koike, H.; Tokoroyama, T. *Tetrahedron Lett.* **1978**, 4531. (i) Tokoroyama, T.; Koike, H.; Hirotsu, K.; Ezaki, Y. *Tetrahedron* **1982**, *38*, 2559.

(6) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Zou, N.; Letcher, R. M. *J. Org. Chem.* **1998**, *63*, 6446.

(7) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579.

(8) Triptophenolide methyl ether (**5**) is also a natural product isolated from TWHf. See ref 3b.

(9) (a) van Heerden, F. R.; van Zyl, J. J.; Rall, G. J. H.; Brandt, E. V.; Roux, D. G. *Tetrahedron Lett.* **1978**, 661. (b) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.

(10) (a) For a review on *ortho*-directed metalation, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (c) Lovely, C. J.; Brueggemeier, R. W. *Tetrahedron Lett.* **1994**, *35*, 8735.

10.1021/jo9919613 CCC: $19.00
Published on Web 03/04/2000

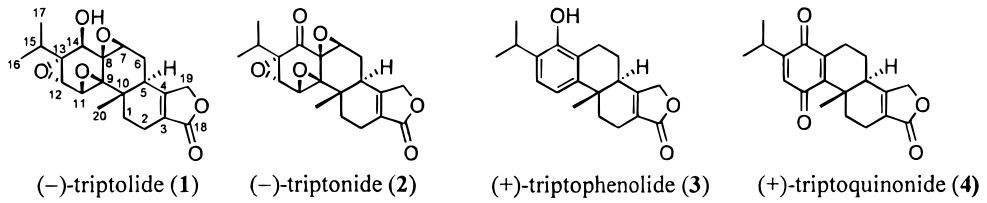
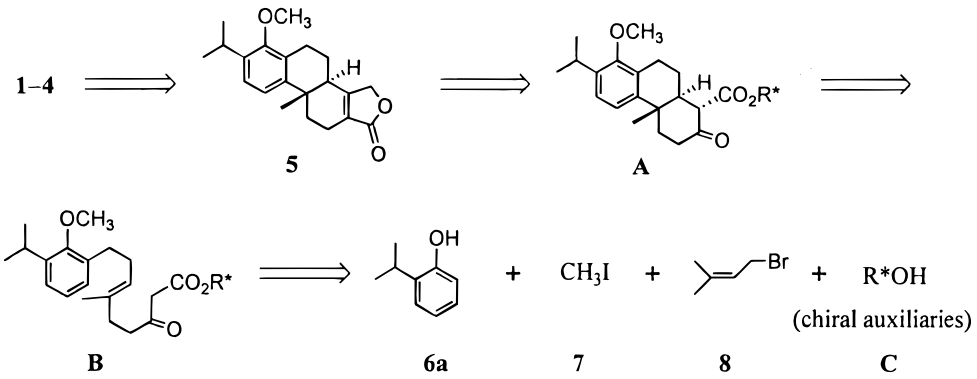
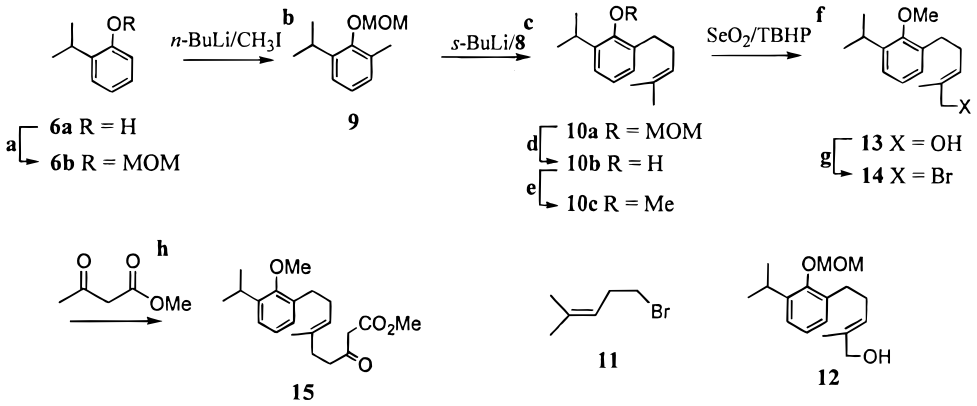


Figure 1.

Scheme 1



Scheme 2[a]



[a] (a) MOMCl, NaH, THF, 65 °C, 2.5 h, 99%; (b) *n*-BuLi, THF, −40 to 20 °C, 2 h, then −78 °C, CH_3I, 1 h, 98%; (c) *s*-BuLi, THF, −78 to −30 °C, 2 h, then −78 °C, **8**, 1 h, 98%; (d) TMSCl, $LiBF_4$, CH_3CN, −10 to 25 °C, 4 h, 97%; (e) Me_2SO_4, K_2CO_3, acetone, reflux, 2.5 h, 100%; (f) SeO_2, *t*-BuO_2H (4.0 equiv), CH_2Cl_2, 0 °C, 8 h, then $NaBH_4$, MeOH, 73%; (g) MsCl, Et_3N, CH_2Cl_2, −40 to −20 °C, 1 h, then LiBr, THF, −20 to 25 °C, 2 h, 96%; (h) $CH_3COCH_2CO_2CH_3$, NaH, *n*-BuLi, THF, 0 °C, 1 h, 85%.

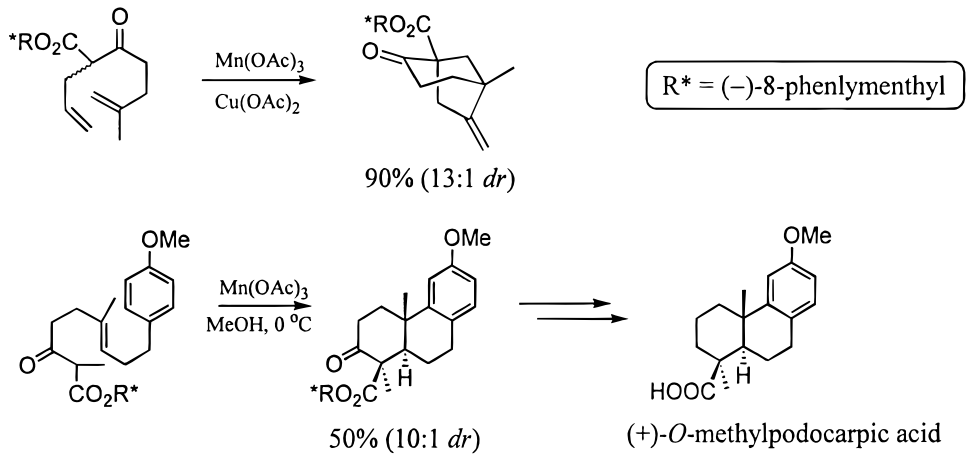
olefin **10a** in 98% yield. However, *ortho* lithiation of **6b** using *s*-BuLi/THF, followed by alkylation with homoallylic bromide **11**, failed to give product **10a**. The allylic oxidation of compound **10a** with SeO_2/TBHP[11] afforded compound **12** in only 25% yield. The protecting group was then changed from MOM ether to methyl ether using TMSCl/$LiBF_4$[12] for deprotection and Me_2SO_4[13] for methylation. Allylic oxidation of **10c** with SeO_2/TBHP provided significant improvement in yield (73%). The allylic alcohol **13** was converted into allylic bromide **14**, and the dianion displacement furnished the acyclic precursor **15**.[14]

2. Preparation of Acyclic Chiral Precursors 17. Recent studies have shown that high diastereoselectivity can be obtained in a number of radical processes.[15] The results from both Snider[16a,b] and Zoretic's labs[16c] revealed that, among those chiral auxiliaries tested in Mn(III)-based asymmetric radical cyclization of β-keto esters, (−)-8-phenylmenthol was the best one with good diastereomer ratio (up to 13:1) and high yield (Scheme 3).[16a,b] Therefore, acyclic precursor **17** was synthesized by ester exchange of **15** with (−)-8-phenylmenthol (**16**) in the presence of a catalytic amount of DMAP (Scheme 4). [17]

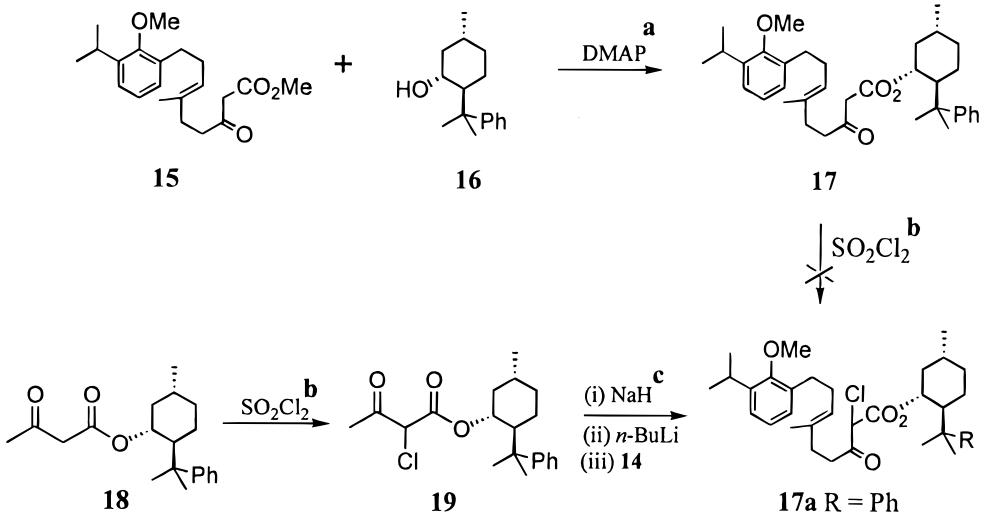
As the α-chloro substituent was shown to increase the reactivity of β-keto esters in radical cyclization reactions,[18] acyclic precursor **17a** was designed (Scheme 4).

(11) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
(12) Yang, D.; Ye, X.-Y. Manuscript in preparation.
(13) Vyas, G. N.; Shah, N. M. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 836.
(14) (a) Axelrod, E. H.; Milne, G. M.; van, Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139. (b) Lee, J. B.; Nolan, T. J. *Can. J. Chem.* **1966**, *44*, 1331. (c) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(15) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
(16) (a) Snider, B. B.; Wan, B. Y.-F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328. (b) Zhang, Q.-W.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640. (c) Zoretic, P. A.; Weng, X.; Biggers, M. S.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637.
(17) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3619.

Scheme 3



Scheme 4[a]



[a] (a) DMAP, toluene, reflux, 90%; (b) SO_2Cl_2, CCl_4, 0 °C to room temperature, overnight, 90%; (c) (i) NaH, THF, 0 °C; (ii) *n*-BuLi, 0 °C; (iii) Bromide **14**; 87%.

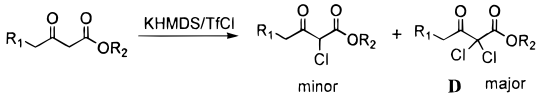
Direct α-chlorination of **17** by the use of SO_2Cl_2[19a−c] or TfCl/base[19d] encountered difficulties.[19e] Therefore, intermediate **19** was prepared by α-chlorination of **18**. Modified dianion displacement[20] with allylic bromide **14** afforded precursor **17a** in good yield.

3. Radical Cyclization in the Absence of Lanthanide Triflates. Initially, the radical cyclization reactions of chiral precursor **17** was performed in the absence of lanthanide triflates (Scheme 5).[21] Cyclization of **17** afforded mainly the trans products **20** and **21** along with a small amount of the cis products **22** and **23**. Since we only focused on the trans products for triptolide synthesis, the absolute configurations and diastereoselectivities of the cis products were not determined. The diastereomer ratio of **20**:**21** was found to be 9.3:1 by ^{1}H NMR analysis of the crude products.

Precursor **17a**, bearing an α-chloro substituent, was more reactive,[18] and the cyclization reaction was carried out in MeOH at 0 °C (Scheme 5). The trans products **24**[22] were isolated in 87% yield. Dechlorination was subsequently carried out with Zn/HOAc.[23] The ^{1}H NMR spectra

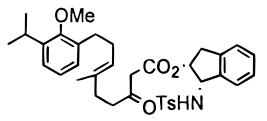
(18) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.

(19) (a) Boehme, W. R. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 590. (b) Wyman, D. P.; Kaufman, P. R.; Freeman, W. R. *J. Org. Chem.* **1964**, *29*, 2706. (c) Kharasch, M. S.; Brown, H. C. *J. Am. Chem. Soc.* **1939**, *61*, 3432. (d) Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, *38*, 3643. (e) Sulfuryl chloride (SO_2Cl_2) was found to react with the C=C double bond, hence interfering with the chlorination process. Attempts to introduce an α-chloro substituent to *β*-keto esters by using TfCl/KHMDS produced dichloro compound **D** as the major product.

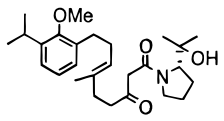


(20) Standard dianion displacement did not give satisfactory yield (ca. 30%). See: Snider, B. B.; McCarthy, B. A. *Tetrahedron* **1993**, *49*, 9447. (b) In our case, the dianion needs to be prepared at −10 to 0 °C for 0.5 h in order to achieve high yield (80−87% yield).

(21) Our initial studies on asymmetric radical cyclization involved the use of the following chiral auxiliaries. Compound **17b** was cyclized into trans products in poor diastereomer ratio (1.2:1 dr). Amide **17c** bearing chiral pyrrolidine auxiliary was cyclized in less than 30% yield. As the cyclization of amides usually affords low chemical yields, the use of chiral amines as auxiliaries in Mn(III)-based oxidative free-radical cyclization becomes extremely limited.

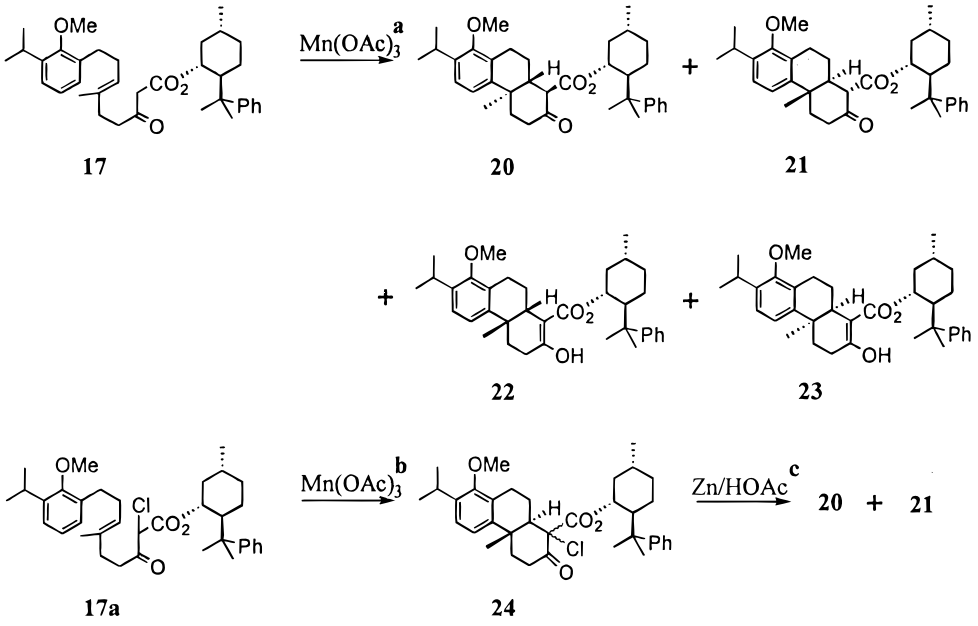


17b



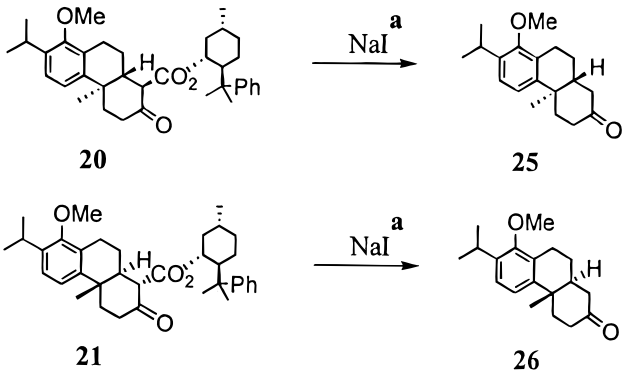
17c

Scheme 5[a]



[a] (a) $Mn(OAc)_3 \cdot 2H_2O$, HOAc, 50 °C, 1 h; 42% of **20** and **21**, 8% of **22** and **23**; (b) $Mn(OAc)_3 \cdot 2H_2O$, MeOH, 0 °C, 10−12 h, 87%; (c) Zn, HOAc, rt, 100%.

Scheme 6[a]



[a] (a) NaI, HMPA−H_2O, 160 °C, overnight, 60%.

of the dechlorinated products **20** and **21** showed that the ratio of these two compounds was 1:5. Compared with the cyclization of **17**, the diastereoselectivity is obviously reversed.

To determine their configurations, the two diastereomers **20** and **21** were converted into the two enantiomers **25** and **26**, respectively, under the decarboxylation conditions (reflux in NaI/HMPA−H_2O) (Scheme 6).[24] The CD spectrum of ketone **25** (derived from **20**) showed a negative Cotton effect at 291.2 nm, corresponding to the n→π* transition of the carbonyl group (for the CD spectra, see Supporting Information).[25a] On the other hand, ketone **26** (derived from **21**) showed a positive Cotton effect at 291.2 nm. The absolute configurations of **25** and **26** were thus deduced from their CD spectra based on the Octant rule.[25b] The configurations of compounds **20** and **21** were unambiguously established by ultimate conversion of compound **21** to the natural (+)-triptophenolide (vide infra).

The contrasting diastereoselectivities in the presence and in the absence of α-chloro substituent seem particularly intriguing, which may shed light on the transition states for radical cyclization reactions. In the absence of an α-substituent, the two carbonyl groups of β-keto ester **17** can adopt the syn or the anti orientation in the transition state (Figure 2). In the syn orientation, the 8-phenyl group on the chiral auxiliary can effectively shield the (si)-face of the radical and restrict the cyclization to the (re)-face to give **20**. In the anti orientation; however, only the (si)-face is accessible for the radical cyclization, providing diastereomer **21**. The fact that **20** was obtained as the major diastereomer suggests that the syn orientation is favorable and the cyclization proceeds through a six-membered ring chairlike transition state with the ester group in the less-hindered equatorial position.

For the cyclization of **17a** with an α-chloro substituent, however, there could be four chairlike transition states (TS1−TS4), differing in the orientation of α-chloro group in respect of the two carbonyl groups (Figure 2). TS3 and TS4, leading to the formation of tricyclic compounds **F** and **G** with the α-chloro group in the axial position, are considered less likely given our previous results on the radical cyclization reactions of achiral β-keo esters containing an α-chloro substituent.[26] In both TS1 and TS2, the menthyl ester group is in the axial position, cis to the angular methyl group. But TS1 suffers from some steric interaction between the methyl substituent on the C=C double bond and 6-CH_2 group of the menthyl

(22) The trans-ring junction products **24** are a mixture of diastereomers, which are inseparable by flash column chromatography. Therefore, the diastereomer ratio was determined after the removal of an α-chloro group.

(23) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1985**, *26*, 4291.

(24) Tsuji, J.; Shimizu, I.; Suzuki, H.; Naito, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5070.

(25) (a) Legrand, M.; Rougier, M. J. In *Stereochemistry: Fundamentals and Methods*; Kagan, H. B., Eds; Georg Thieme: Stuttgart, 1977; Vol. 2, pp 118−122. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 1022−1033.

(26) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc*,. in press.

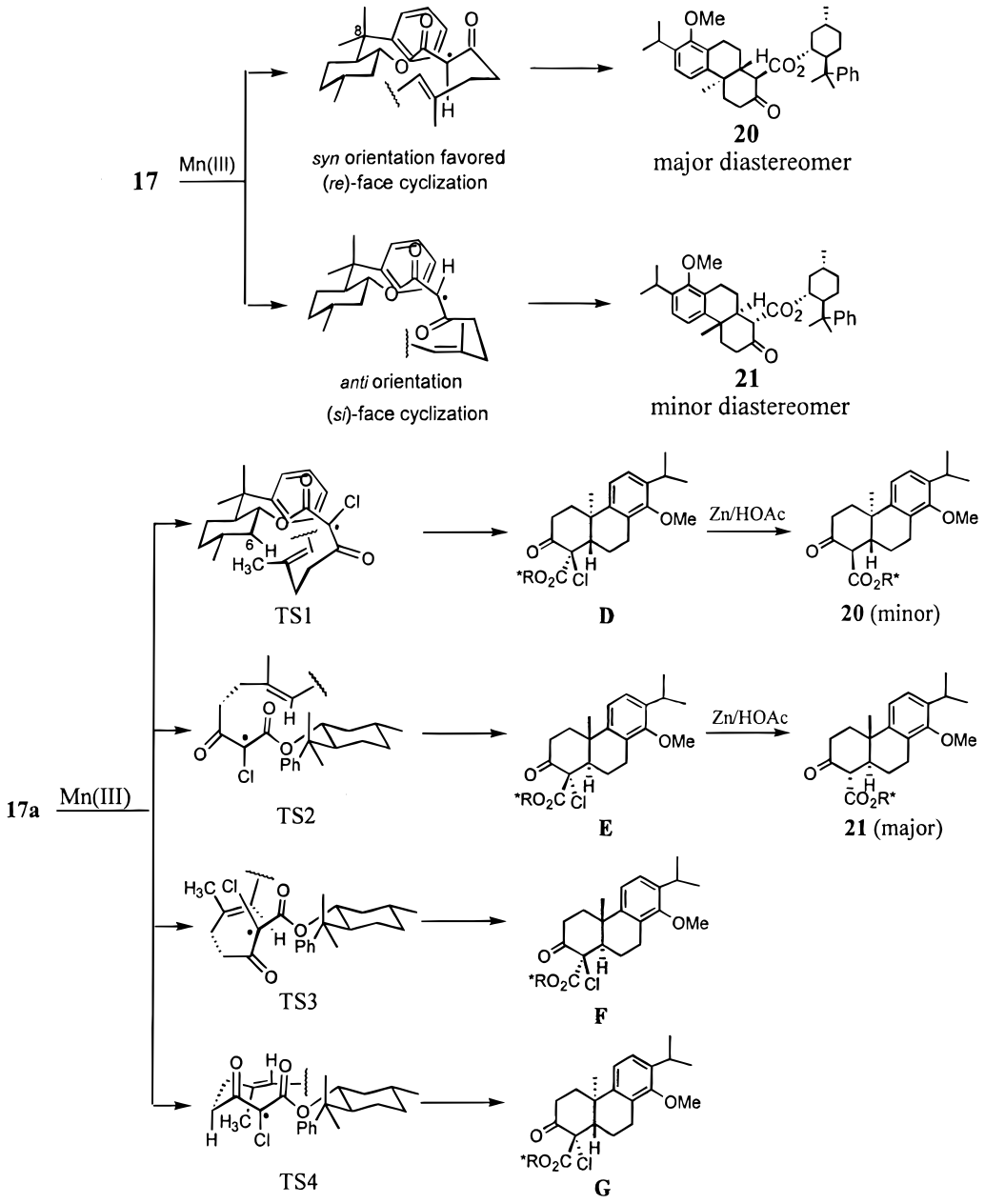
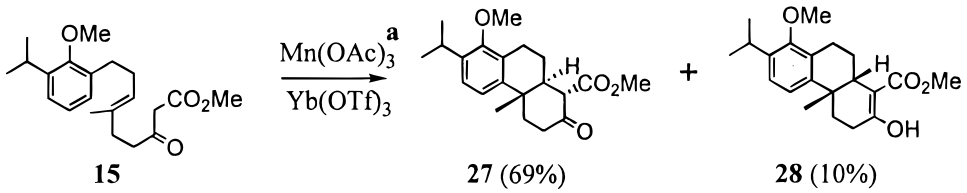


Figure 2.

Scheme 7[a]



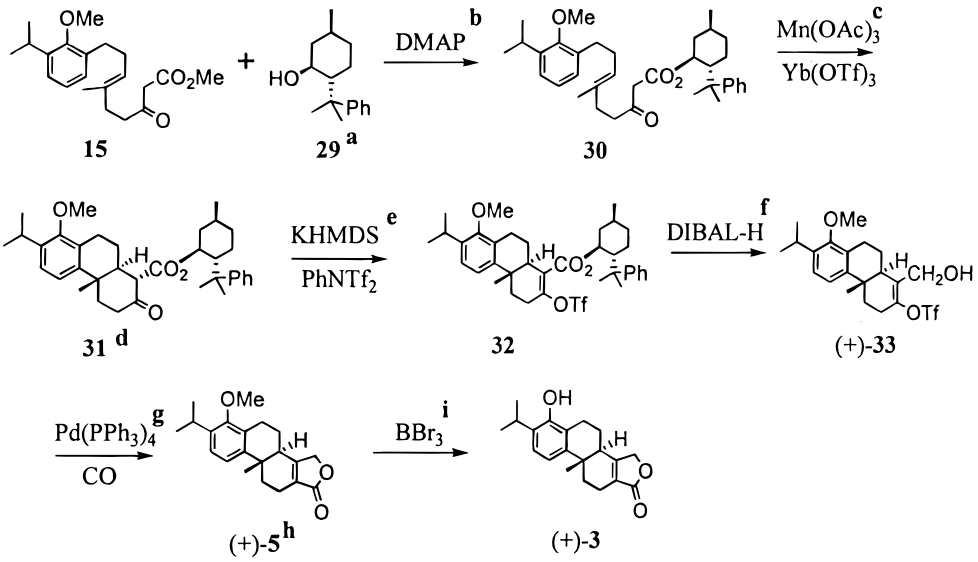
[a] (a) $Mn(OAc)_3 \cdot 2H_2O$, $Yb(OTf)_3$ (1 equiv), CF_3CH_2OH, 0 °C, 3 h.

moiety. Therefore, TS2 becomes the most favorable transition state, and cyclization of **17a** would give product **E** as the major diastereomer. HPLC purification of cyclization products **24** confirms that **E** is the most abundant product whereas **D** is less. Upon dechlorination of **24**,[23] **21** was thus obtained as major diastereomer.

4. Radical Cyclization in the Presence of Lanthanide Triflates. Recently, we found that lanthanide triflates can catalyze the Mn(III)-based radical cyclization reactions through their strong chelation to the β-keto ester group.[7,26] In the presence of $Ln(OTf)_3$, the cyclization reactions were accelerated and the trans/cis ratios were improved (Scheme 7). The results of asymmetric radical cyclization of compound **17** in the presence of lanthanide triflates are summarized in Table 1.[27]

(27) In the presence of lanthanide triflates, acyclic precursor **17a** was decomposed.

Scheme 8[a]



[a] (a) Reference 30; (b) DMAP, toluene, reflux, 90%; (c) $Mn(OAc)_3 \cdot 2H_2O$, $Yb(OTf)_3$ (1 equiv), CF_3CH_2OH, −5 °C, 5 h, 73%; (d) diastereomer ratio was determined by NMR to be 38:1; (e) KHMDS, THF, −78 to −20 °C, then $PhNTf_2$, −78 °C to room temperature, 95%; (f) DIBAL-H (2.2 equiv), CH_2Cl_2, −78 to −30 °C, 20 h, 63% (with 26% recovery of starting material); (g) Bu_3N, $Pd(PPh_3)_4$, LiCl, CO (1 atm), CH_3CN, 65 °C, 12 h, 93%; (h) >99% ee by HPLC analysis; (i) BBr_3, CH_2Cl_2, −78 °C to room temperature, 99%.

Table 1. $Ln(OTf)_3$-Promoted Asymmetric Radical Cyclization Reactions of 17 Mediated by $Mn(OAc)_3 \cdot 2H_2O$[a]

entry	substrate	$Ln(OTf)_3$ (equiv)	yield[b] (%)	diastereomer ratio (**20**:**21**)[c]
1	**17**	$Yb(OTf)_3 \cdot H_2O$ (1.0)	77	38:1
2	**17**	$Yb(OTf)_3 \cdot H_2O$ (0.2)	71	26:1
3	**17**	$Sm(OTf)_3$ (0.2)	73	28:1
4	**17**	$Pr(OTf)_3$ (0.2)	76	24:1
5	**17**	$Eu(OTf)_3$ (0.2)	68	26:1

[a] Unless otherwise indicated, all reactions were carried out in degassed CF_3CH_2OH at 0.05 M concentration with 2.2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ at −5 °C. [b] Isolated yield. [c] Determined by ^1H NMR analysis (500 MHz, $CDCl_3$) of the crude residues.

We found that the cyclization of **17** in the presence of $Yb(OTf)_3 \cdot H_2O$ (1 equiv) in CF_3CH_2OH at −5 °C afforded the trans products **20** and **21** in a significantly higher diastereomer ratio (38:1) as well as higher yield (77%). It is worth noticing that the use of a catalytic amount of $Yb(OTf)_3$ did not lead to a significant decrease in diastereoselectivity (entry 1 vs entry 2). Besides $Yb(OTf)_3$, other lanthanide triflates such as $Sm(OTf)_3$, $Eu(OTf)_3$, and $Pr(OTf)_3$ were also examined as catalysts in the asymmetric radical cyclization of **17**, and similar diastereoselectivities were observed (entries 3−5).

The effect of lanthanide triflates on radical cyclization of (−)-8-phenylmenthyl ester **17** can be explained using chairlike transition states shown in Figure 2. As the bidentate chelation of the β-keto ester to $Ln(OTf)_3$ would lock the two carbonyl groups in the syn orientation, the diastereoselectivity is expected to be dramatically improved, favoring the formation of **20**. The excellent chiral induction suggests the importance of Lewis acids in controlling the carbonyl rotamer population in the cyclization step.[28]

5. Enantioselective Synthesis of (−)-Triptolide, (−)-Triptonide, (+)-Triptophenolide, and (+)-Triptoquinonide. The use of (−)-8-phenylmenthol as chiral auxiliary in radical cyclization of **17** provided the trans product **20** in 77% yield with a 38:1 dr. However, the major diastereomer **20** has an undesired absolute configuration for (−)-triptolide synthesis. Though the radical cyclization of **17a** followed by dechlorination afforded **21** as the major diastereomer, the dr was lower (5:1). Therefore, (+)-8-phenylmenthol was used as the chiral auxiliary for the synthesis of (−)-triptolide.

(+)-8-Phenylmenthol (**29**) was synthesized following the literature procedure.[29] Ester exchange in the presence of a catalytic amount of DMAP provided acyclic precursor **30** (Scheme 8). The cyclization of **30** afforded the major diastereomer **31** (the enantiomer of **20**) in 73% yield (38:1 dr).

Crisp's method[30] was applied to the construction of α,β-unsaturated γ-lactone from tricyclic compound **31**. Vinyl triflate **32** was readily prepared in 95% yield. The reduction of **32** was performed by using 2.2 equiv of DIBAL-H in dichloromethane at −78 to −30 °C for 20 h, affording allylic alcohol (+)-**33** (63% isolated yield, 85% yield based on the recovered starting material). The carbonylation of (+)-**33** under standard conditions produced (+)-triptophenolide methyl ether [(+)-**5**] in 93% yield. The HPLC analysis of **5** showed that >99% ee was achieved (see Supporting Information). Subsequent deprotection of (+)-**5** afforded (+)-**3** almost quantitatively . This compound showed a positive value of specific optical rotation, i.e. $[\alpha]^{20}_D = +35.3°$ (*c* 0.17, $CHCl_3$), suggesting that it has the same absolute configuration as the natural (+)-triptophenolide [lit.[31] +30 ° (*c* 0.29, $CHCl_3$)].

With the key intermediate (+)-**5** in hand, we accomplished the remaining steps toward (−)-triptolide and (−)-triptonide by following our procedure for the synthesis of (±)-triptolide (Scheme 9).[6] The synthesized (−)-triptonide [(−)-**2**] showed the identical NMR spectra and optical rotation to the data reported in the literature.[3a]

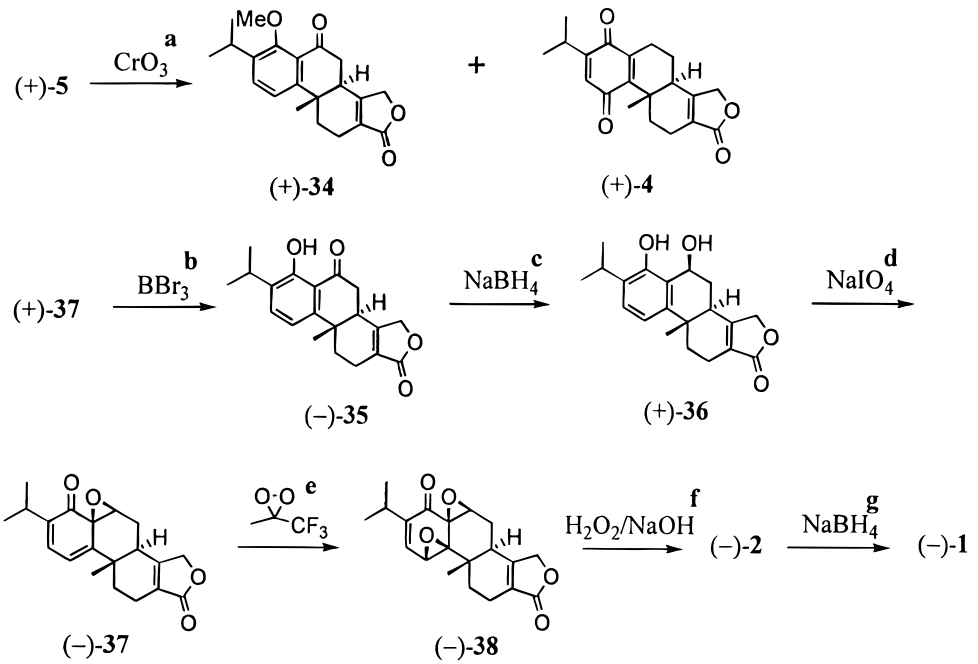
(28) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

(29) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380. (c) Buschmann, H.; Scharf, H.-D. *Synthesis* **1988**, 827.

(30) Crisp, G. T.; Meyer A. G. *J. Org. Chem.* **1992**, *57*, 6972.

(31) Wu, D.-G.; Sun, X.-C.; Li, F. *Acta Bot. Yunnanica* **1979**, *1*, 29.

Scheme 9[a]



[a] (a) CrO_3, HOAc (aq), rt, 45% of (+)-**34**, 15% of (+)-**4**; (b) BBr_3, CH_2Cl_2, −78 °C to room temperature, 99%; (c) $NaBH_4$, CH_3OH, 0 °C, 2 h, 99%; (d) $NaIO_4$, 3:1 CH_3OH:H_2O, 0 to 25 °C, 1 h, 96%; (e) CF_3COCH_3, Oxone, $NaHCO_3$, 3:2 CH_3CN:aq Na_2(EDTA), 25 °C, 4 h, 70%; (f) H_2O_2, NaOH, MeOH, 25 °C, 3 h, 96%; (g) Eu(FOD)$_3$, $NaBH_4$, CH_3OH, 49%.

The CD spectrum is exactly the same as that of the authentic sample.[32] In view of the prior conversion of (±)-triptonide to (±)-triptolide, a total synthesis of (−)-triptolide [(−)-**1**] was thus accomplished.

The oxidation step from (+)-**5** to (+)-**34** by CrO_3/HOAc−H_2O produced 15% of triptoquinonide (+)-**4** as a minor product (Scheme 9). The specific optical rotation of (+)-**4**, i.e. $[\alpha]^{20}_D = +110.1°$ (*c* 0.2, $CHCl_3$), is almost identical to the literature report [lit.[3c]: $[\alpha]^{26}_D = +110.3°$ (*c* 0.28, $CHCl_3$)].

Conclusion

In summary, we have completed the first enantioselective synthesis of (−)-triptolide (**1**), (−)-triptonide (**2**), (+)-triptophenolide (**3**), and (+)-triptoquinonide (**4**) by using a Yb(OTf)$_3$-catalyzed asymmetric oxidative radical cyclization method. While (+)-8-phenylmenthol proved to be an effective chiral auxiliary in our hand, it is worthwhile to explore other chiral auxiliaries which give excellent chiral induction for both enantiomers of polycyclic products. In addition, our asymmetric oxidative radical cyclization method will be applied to asymmetric synthesis of many polycyclic natural products as well as chiral triptolide analogues.

Experimental Section

Preparation of Chiral Acyclic Precursor 17. A solution of **15** (346 mg, 1.0 mmol), (−)-8-phenylmenthol **16** (232 mg, 1.0 mmol), and 4-(dimethylamino)pyridine (36.6 mg, 0.3 mmol) in dry toluene (15 mL) was refluxed for 20 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford compound **17** (518 mg, 0.95 mmol, 95% yield) as colorless oil. $[\alpha]^{20}_D = +14.4°$ (*c* 1.13, CH_2Cl_2); analytical TLC (silica gel 60), 10% EtOAc in *n*-hexane, $R_f = 0.36$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.10 (s, 0.08 × 1H), 7.27−6.97 (m, 8H), 5.20 (apparent t, $J = 6.1$ Hz, 1H), 4.82 (dt, $J = 4.3$, 10.7 Hz, 1H), 4.40 (s, 0.08 × 1H), 3.72 (s, 3H), 3.33 (sept, $J = 6.9$ Hz, 1H), 2.77 (d, $J = 15.7$ Hz, 0.92 × 1H), 2.65 (d, $J = 15.7$ Hz, 0.92 × 1H), 2.63 (m, 2H), 2.47−2.37 (m, 2H), 2.37−1.55 (m, 10H), 1.53 (s, 3H), 1.50−1.37 (m, 1H), 1.30 (s, 3H), 1.22 (d, $J = 6.9$ Hz, 6H), 1.20−1.00 (m, 1H), 1.18 (s, 3H), 0.87 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 166.3, 155.3, 151.6, 141.5, 134.6, 133.6, 127.7, 127.3, 125.1, 124.8, 124.4, 124.2, 124.0, 74.7, 61.4, 49.9, 48.7, 41.6, 41.3, 41.2, 39.2, 34.3, 32.7, 31.0, 29.9, 28.8, 26.6, 26.5, 26.1, 23.8, 23.2, 21.6, 15.7; IR (CH_2Cl_2) 1733, 1714 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{50}O_4$ (M^+): 546.3709, found 546.3710; LRMS (EI, 20 eV) *m*/*z* 546 (M^+, 1), 314 (44), 119 (90), 105 (100). Anal. Calcd for $C_{36}H_{50}O_4$: C, 79.08; H, 9.22. Found: C, 79.00; H, 9.33.

Preparation of (−)-8-Phenylmenthyl 2-Chloroacetoacetate (19). To a solution of (−)-8-phenylmenthyl acetoacetate (1.31 g, 4.14 mmol) in CCl_4 (1 mL) at 0 °C was added sulfuryl chloride (0.34 mL, 4.14 mmol) dropwise. The mixture was gradually warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure at 45−50 °C. The residual dark-amber liquid was purified by flash column chromatography to afford compound **19** (1.31 g, 90% yield) as slightly yellow oil; $[\alpha]^{20}_D = +19.1°$ (*c* 0.744, CH_2Cl_2); analytical TLC (silica gel 60), 10% EtOAc in *n*-hexane, $R_f = 0.38$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 0.51 × 1H, enol), 7.34−7.10 (m, 5H), 4.96−4.80 (m, 1H), 3.98 (s, 0.18 × 1H, ketone 1), 3.53 (s, 0.31 × 1H, ketone 2), 2.28 (s, 0.18 × 3H, ketone 1), 2.13 (s, 0.51 × 3H, enol), 2.11 (s, 0.31 × 3H, ketone 2), 2.08−0.84 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7 (ketone 1), 196.0 (ketone 2), 172.1, 168.4, 164.6, 163.6, 151.7, 150.9, 150.0, 128.1, 128.0, 127.9, 125.6, 125.5, 125.1, 97.5, 77.6, 77.0, 76.4, 61.3, 60.1, 50.5, 50.4, 50.1, 41.7, 41.0, 40.9, 40.1, 39.4, 34.4, 31.4, 31.3, 31.2, 29.6, 28.7, 27.5, 27.1, 26.6, 26.2, 25.5, 25.2, 22.7, 21.7, 21.6, 19.7; IR (CH_2Cl_2) 1730, 1628 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{27}ClO_3$ (M^+): 350.1647, found 350.1648; LRMS (EI, 70 eV) *m*/*z* 350 (M^+, 2), 119 (100).

Preparation of Compound 17a. To a suspension of sodium hydride (60% in mineral oil, 48 mg, 1.20 mmol) in dry THF (3 mL) at −10 °C was added (−)-8-phenylmenthyl 2-chloroacetoacetate (350 mg, 1.00 mmol) in THF (3 mL)

(32) The authentic sample of (−)-triptonide (**2**) was obtained from Shanghai Institute of Materia Medica, Academia Sinica, P. R. China.

dropwise. After 10 min, *n*-butyllithium (1.60 M, 0.69 mL, 1.10 mmol) was added to the mixture slowly. The solution was stirred at −10 °C for 30 min. A solution of allylic bromide **14** (327 mg, 1.05 mmol) in THF (5 mL) was transferred into the above mixture via a cannula, and the reaction was stirred at −10 °C for another 1.5 h. Saturated ammonium chloride solution was added to quench the reaction. The resulting mixture was extracted with dichloromethane. The extracts were dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography to afford compound **17a** (504 mg, 0.87 mmol, 87% yield) as colorless oil. $[\alpha]^{20}_D = +12.4°$ (*c* 1.22, CH_2Cl_2); analytical TLC (silica gel 60), 10% EtOAc in *n*-hexane, R_f = 0.44; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 0.36 × 1H, enol), 6.32−6.98 (m, 8H), 5.32−5.16 (m, 1H), 4.94−4.84 (m, 1H), 4.07 (s, 0.21 × 1H, ketone 1), 3.71 (s, 0.36 × 3H, enol), 3.70 (s, 0.64 × 3H, ketones 1 & 2), 3.54 (s, 0.42 × 1H, ketone 2), 3.32 (sept, *J* = 6.9 Hz, 1H), 2.73−0.82 (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4 (ketone 1), 198.1, (ketone 2), 174.9, 168.5, 165.0, 163.6, 155.5, 151.9, 150.8, 150.0, 141.6, 134.7, 133.8, 133.3, 128.0, 127.9, 127.4, 125.5, 125.4, 125.3, 125.2, 125.1, 125.0, 124.3, 124.1, 97.0, 77.5, 76.7, 76.3, 61.5, 60.5, 59.8, 50.4, 50.3, 50.0, 41.6, 40.9, 40.8, 40.0, 39.6, 39.2, 37.9, 37.8, 35.3, 34.3, 33.0, 31.9, 31.5, 31.3, 31.2, 31.1, 30.1, 29.8, 29.1, 29.0, 27.2, 27.0, 26.6, 26.3, 26.0, 25.8, 23.9, 22.6, 22.1, 21.6, 15.8, 15.7; IR (CH_2Cl_2) 1754, 1727 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{49}ClO_4$ (M^+): 580.3319; found 580.3314; LRMS (EI, 70 eV) *m*/*z* 580 (M^+, 1), 119 (91), 105 (100). Anal. Calcd for $C_{36}H_{49}ClO_4$: C, 74.39; H, 8.50. Found: C, 74.65; H, 8.81.

Mn(III)-Based Oxidative Free-Radical Cyclization of 17 in the Absence of Lewis Acids. To a solution of acyclic precursor **17** (163.8 mg, 0.30 mmol) in acetic acid (3 mL) was added $Mn(OAc)_3 \cdot 2H_2O$ (182.3 mg, 0.66 mmol) under argon. The mixture was stirred at 50 °C. The color of the mixture turned to white after 1 h. Saturated $NaHSO_3$ solution was added to the mixture followed by extraction with CH_2Cl_2. The extract was dried with anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (5% to 10% EtOAc in *n*-hexane) to afford trans-ring junction products **20** and **21** (68.6 mg, 42% yield) and cis-ring junction products **22** and **23** (13.1 mg, 8% yield). The ratio of **20**:**21** was determined by ^{1}H NMR (500 MHz, $CDCl_3$) analysis. Diastereomers **20** and **21** were separated by preparative HPLC (silica gel column, eluting solvent 4% *i*-PrOH in *n*-hexane, flow rate 8 mL/min).

20: white solid, mp 84−86 °C (MeOH); analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.47; $[\alpha]^{20}_D = -49.8°$ (*c* 0.11, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.02 (m, 7H), 4.77 (dt, *J* = 3.9, 10.6 Hz, 1H), 3.67 (s, 3H), 3.27 (sept, *J* = 6.9 Hz, 1H), 2.93 (apparent dd, *J* = 4.0, 17.6 Hz, 1H), 2.69−2.63 (ddd, *J* = 8.0, 10.7, 18.5 Hz, 1H), 2.51 (m, 3H), 2.30−2.15 (m, 3H), 2.05 (m, 1H), 1.83 (m, 1H) 1.75−1.45 (m, 6H), 1.35 (s, 3H), 1.24 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.18 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 1.15−0.83 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 205.1, 169.3, 155.0, 152.0, 143.8, 139.0, 128.4, 127.5, 125.8, 124.6, 124.0, 120.9, 60.4, 59.4, 50.4, 44.8, 41.3, 39.6, 38.0, 37.1, 36.1, 34.7, 31.3, 30.9, 27.3, 26.6, 26.0, 25.0, 23.9, 23.8, 23.8, 23.1, 22.0, 21.8; IR (CH_2Cl_2) 1733, 1730 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{48}O_4$ (M^+): 544.3552, found 544.3564; LRMS (EI, 20 eV) *m*/*z* 544 (M^+, 21), 426 (100), 214 (50), 119 (63). Anal. Calcd for $C_{36}H_{48}O_4$: C, 79.37; H, 8.88. Found: C, 79.37; H, 9.01.

21: white solid, mp 91−93 °C (EtOAc/*n*-hexane); analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.47; $[\alpha]^{20}_D = +60.8°$ (*c* 0.074, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.05 (m, 3H), 4.81 (dt, *J* = 4.0, 10.7 Hz, 1H), 3.72 (s, 3H), 3.30 (sept, *J* = 6.9 Hz, 1H), 3.03 (apparent dd, *J* = 4.0, 17.6 Hz, 1H), 2.75 (m, 1H), 2.65 (d, *J* = 13.1 Hz, 1H), 2.60−2.30 (m, 3H), 2.30−2.07 (m, 2H), 1.84−1.35 (m, 7H), 1.31 (s, 3H), 1.25 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.21 (s, 3H), 1.15−0.83 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 168.8, 155.2, 152.1, 144.1, 139.0, 128.6, 127.9, 125.5, 124.7, 124.0, 120.8, 76.0, 60.5, 59.2, 44.0, 41.1, 39.6, 38.1, 37.5, 36.2, 34.8, 31.4, 28.3, 26.6, 26.2, 24.6, 24.2, 24.0, 24.0, 23.8, 23.6, 22.4, 21.8; IR (CH_2Cl_2) 1732, 1703 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{48}O_4$ (M^+): 544.3553, found 544.3553; LRMS (EI, 70 eV) *m*/*z* 544 (M^+, 17), 426 (42), 214 (26), 119 (100). Anal. Calcd for $C_{36}H_{48}O_4$: C, 79.37; H, 8.88. Found: C, 79.37; H, 9.22.

Mn(III)-Based Oxidative Free-Radical Cyclization of 17a. To a solution of acyclic precursor **17a** (116 mg, 0.20 mmol) in degassed CH_3OH (2 mL) was added $Mn(OAc)_3 \cdot 2H_2O$ (118 mg, 0.44 mmol) in one portion at 0 °C. The reaction was stirred at 0 °C for 14 h. Saturated $NaHSO_3$ solution was added to the mixture followed by extraction with CH_2Cl_2. The extracts were dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford trans-ring junction products **24** (99 mg, 0.17 mmol, 85% yield) as a white solid. Diastereomers **24** were separated by preparative HPLC (Chiralcel OD column, eluting solvent 1% *i*-PrOH in *n*-hexane, flow rate 5 mL/min) to afford **D** and **E** as major compounds (**E** was more abundant than **D**).

D: White solid, mp 201−202 °C (CH_2Cl_2); $[\alpha]^{20}_D = -54.8°$ (*c* 0.42, CH_2Cl_2); analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.13 (m, 5H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 4.92 (dt, *J* = 4.4, 10.7 Hz, 1H), 3.72 (s, 3H), 3.30 (sept, *J* = 6.9 Hz, 1H), 3.16 (m, 1H), 3.04 (dt, *J* = 5.8, 13.7 Hz, 1H), 2.83 (dq, *J* = 2.5, 14.4 Hz, 1H), 2.75−2.28 (m, 4H), 2.11−1.70 (m, 3H), 1.53−1.42 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H), 1.32−1.20 (m, 4H), 1.27 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.10 (m, 1H), 0.93 (m, 1H), 0.85 (d, *J* = 6.2 Hz, 1H), 0.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 165.9, 155.1, 149.7, 144.1, 139.2, 128.6, 128.0, 125.9, 125.4, 124.3, 121.1, 78.3, 78.0, 60.6, 56.6, 50.7, 40.9, 40.4, 39.7, 39.2, 37.7, 34.1, 31.7, 31.3, 30.9, 27.5, 26.1, 23.9, 23.8, 23.8, 22.5, 21.7, 21.3; IR (CH_2Cl_2) 1749, 1731 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{47}ClO_4$ (M^+): 578.3163, found 578.3155; LRMS (EI, 20 eV) *m*/*z* 578 (M^+, 4), 214 (17), 119 (100).

E: White solid, mp 86−89 °C (Et_2O/*n*-hexane); $[\alpha]^{20}_D = +51.2°$ (*c* 0.09, CH_2Cl_2); analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.15 (m, 5H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 4.88 (dt, *J* = 4.2, 10.6 Hz, 1H), 3.73 (s, 3H), 3.30 (sept, *J* = 6.9 Hz, 1H), 3.17 (m, 1H), 3.08 (dt, *J* = 6.1, 15.0 Hz, 1H), 2.78 (dq, *J* = 2.4, 14.9 Hz, 1H), 2.72−2.46 (m, 3H), 2.25−2.08 (m, 4H), 1.93 (dt, *J* = 3.6, 14.3 Hz, 1H), 1.84 (dt, *J* = 4.2, 14.8 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H), 1.27 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.08−0.85 (m, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.74 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.5, 167.7, 154.9, 149.9, 144.2, 139.2, 128.5, 128.1, 125.8, 125.5, 124.4, 121.1, 79.6, 78.5, 60.5, 55.9, 50.4, 41.1, 40.3, 39.6, 38.7, 37.6, 34.2, 31.5, 31.4, 31.0, 30.9, 27.7, 26.1, 26.0, 23.9, 23.7, 23.6, 21.8, 21.7; IR (CH_2Cl_2) 1741, 1707 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{47}ClO_4$ (M^+): 578.3163, found 578.3168; LRMS (EI, 20 eV) *m*/*z* 578 (M^+, 2), 119 (100).

Mn(III)-Based Oxidative Radical Cyclization of 17 in the Presence of Lewis Acids. To a solution of acyclic precursor **17** (54.6 mg, 0.10 mmol) in degassed CF_3CH_2OH (1 mL) was added $Yb(OTf)_3 \cdot H_2O$ (62.0 mg, 0.10 mmol) under argon atmosphere. The mixture was stirred at room temperature for 10 min and then cooled to −5 °C. $Mn(OAc)_3 \cdot 2H_2O$ (60.8 mg, 0.22 mmol) was added in one portion. The reaction was monitored by TLC. Saturated $NaHSO_3$ solution was added to the mixture followed by extraction with CH_2Cl_2. The extracts were dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (5% to 10% EtOAc in *n*-hexane) to afford trans-ring junction products **20** and **21** (41.9 mg, 77% yield) and trace amount of cis-ring junction products **22** and **23**.

Preparation of Compound 30. The procedure for the preparation of **17** was followed. Compound **30**: colorless oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.57; $[\alpha]^{20}_D = -14.2°$ (*c* 1.05, CH_2Cl_2); HRMS (EI) calcd for $C_{36}H_{50}O_4$ (M^+): 546.3709, found 546.3705; LRMS (EI, 20 eV) *m*/*z* 546 (M^+, 12), 163 (42), 119 (100), 105 (94). Anal. Calcd for $C_{36}H_{50}O_4$: C, 79.08; H, 9.22. Found: C, 79.20; H, 9.50. For other characterization data, see those of **17**.

Preparation of Compound 31. The procedure for the preparation of **20** in the presence of $Yb(OTf)_3$ was followed. Compound **31**: white solid, mp 87−89 °C (EtOH/*n*-hexane);

analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.47; $[\alpha]^{20}_D$ = +47.2° (*c* 0.31, CH_2Cl_2); HRMS (EI) calcd for $C_{36}H_{48}O_4$ (M^+): 544.3552, found 544.3552; LRMS (EI, 20 eV) *m*/*z* 545 (M^++1, 21), 544 (M^+, 45), 426 (58), 119 (100). Anal. Calcd for $C_{36}H_{48}O_4$: C, 79.37; H, 8.88. Found: C, 78.99; H, 8.86. For other characterization data see those of **20**.

Preparation of Vinyl Triflate 32. To a solution of compound **31** (2.177 g, 4.0 mmol) in dry THF (100 mL) at −78 °C was added KHMDS (9.6 mL, 4.8 mmol, 0.5 M in toluene) dropwise. The mixture was warmed to −20 °C in a period of 2 h and then cooled to −78 °C. To the above solution, $PhNTf_2$ (1.73 g, 4.8 mmol) was added, and the mixture was warmed to room temperature overnight. The mixture was diluted with CH_2Cl_2 and washed with water followed by a citric acid solution (10%). The organic layers were dried and concentrated. The residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to afford compound **32** (2.57 g, 95% yield) as a colorless oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.65; $[\alpha]^{20}_D$ = +35.2° (*c* 0.051, *n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.00 (m, 7H), 4.91 (dt, *J* = 4.1, 10.6 Hz, 1H), 3.71 (s, 3H), 3.29 (sept, *J* = 6.9 Hz, 1H), 3.02 (apparent dd, *J* = 4.2, 17.8 Hz, 1H), 2.80 (m, 1H), 2.58 (m, 2H), 2.40 (dd, *J* = 5.5, 12.5 Hz, 1H), 2.33−1.40 (m, 8H), 1.34 (s, 3H), 1.26 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 3H), 0.88 (d, *J* = 6.2 Hz, 3H), 1.20−0.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 155.3, 150.9, 145.3, 143.4, 139.2, 128.2, 128.0, 127.9, 125.5, 125.2, 124.0, 120.0, 116.1 (q, *J* = 320 Hz), 60.5, 49.9, 41.3, 41.0, 40.2, 34.4, 33.2, 32.3, 31.4, 28.6, 27.2, 26.1, 24.7, 24.7, 23.9, 23.8, 23.3, 22.1, 21.7, 21.2, 20.3; IR (CH_2Cl_2) 3084, 1715, 1416, 1140 cm^{-1}; HRMS (EI) calcd for $C_{37}H_{47}F_3O_6S$ (M^+): 676.3045, found 676.3041; LRMS (EI, 20 eV) *m*/*z* 676 (M^+, 31), 558 (100).

Reduction of 32 into Allylic Alcohol (+)-33. To a solution of **32** (67.7 mg, 0.1 mmol) in dichloromethane (2.5 mL) at −78 °C was added dropwise diisobutylaluminum hydride (1.0 M solution in toluene, 0.22 mL, 0.22 mmol). The solution was stirred at −30 °C for 20 h. The mixture was washed with water, dried, and concentrated. The crude residue was purified by flash column chromatography (20% EtOAc in *n*-hexane) to afford starting material **32** (17.6 mg, 74% conversion) and compound (+)-**33** (28.2 mg, 63% yield) as a white solid, mp 123−125 °C (CH_2Cl_2/*n*-hexane); analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.37; $[\alpha]^{20}_D$ = +46.5° (*c* 1.36, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 4.42 (dd, *J* = 4.1, 12.4 Hz, 1H), 4.24 (dd, *J* = 4.1, 12.4 Hz, 1H), 3.72 (s, 3H), 3.29 (sept, *J* = 6.9 Hz, 1H), 3.10−1.60 (m, 10H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 144.9, 144.0, 139.0, 130.6, 128.4, 123.8, 120.4 (q, *J* = 320 Hz), 120.0, 60.4, 56.9, 42.5, 35.7, 33.4, 26.1, 25.7, 23.9, 23.8, 23.7, 22.2, 19.9; IR (CH_2Cl_2) 3692, 3605, 3067 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{27}F_3O_5S$ (M^+): 448.1531, found 448.1531; LRMS (EI, 20 eV) *m*/*z* 448 (M^+, 100).

Preparation of Triptophenolide Methyl Ether (+)-5. Carbon monoxide was bubbled through a mixture of **33** (86.5 mg, 0.194 mmol), $Pd(PPh_3)_4$ (22 mg, 0.02 mmol), tri-*n*-butylamine (0.090 mL, 0.388 mmol), and lithium chloride (8.4 mg, 0.194 mmol) in acetonitrile (2 mL) for 20 min. The mixture was heated to 65 °C under 1 atm of carbon monoxide (balloon placed over the reflux condenser) overnight. Diethyl ether was added to the cooled solution, and the mixture was filtered through a pad of Celite and rinsed with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (35% EtOAc in *n*-hexane) to give (+)-**5** (58.8 mg, 93%) as a white solid, mp 174−175 °C (EtOAc/*n*-hexane) [lit.[5d] 175.5−176 °C; lit.[5b] 162−162.5 °C]; analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f = 0.36; >99% ee (determined by HPLC analysis, see Supporting Information), $[\alpha]^{20}_D$ = +40.3° (*c* 0.37, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 2H), 4.79 (m, 2H), 3.73 (s, 3H), 3.30 (sept, *J* = 6.9 Hz, 1H), 3.15−2.85 (m, 2H), 2.80−1.60 (m, 7H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 163.0, 155.4, 144.1, 139.2, 128.0, 124.9, 124.1, 120.2, 70.4, 60.5, 41.1, 36.4, 32.7, 26.1, 23.9, 23.8, 22.7, 22.2, 19.7, 18.2; IR (CH_2Cl_2) 1751, 1680 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}O_3$ (M^+): 326.1882, found 326.1881; LRMS (EI, 20 eV) *m*/*z* 326 (M^+, 97), 311 (100).

Synthesis of (+)-Triptophenolide [(+)-3]. To a solution of (+)-**5** (30.4 mg, 0.093 mmol) in dichloromethane (1.0 mL) at −78 °C was added BBr_3 (1 M in dichloromethane, 0.103 mL, 0.103 mmol) dropwise. The reaction mixture was gradually warmed to room temperature in 2 h. Ice−water (5 mL) was added followed by HCl solution (2 N, 0.5 mL). The mixture was stirred at room temperature for 0.5 h and then extracted with CH_2Cl_2. The extracts were dried and concentrated. The crude product was purified by flash column chromatography to afford (+)-**3** (28.7 mg, 99% yield) as a white solid, mp 214−215 °C (Et_2O/*n*-hexane) [lit.[3b] 232−233 °C]; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.54; $[\alpha]^{20}_D$ = +35.3° (*c* 0.17, $CHCl_3$) [lit.[31] +30° (*c* 0.29, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 4.80 (m, 2H), 4.79 (br., 1H), 3.10 (sept, *J* = 6.9 Hz, 1H), 2.95−1.60 (m, 9H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.2, 162.8, 150.7, 143.8, 130.9, 125.1, 123.4, 120.4, 116.3, 70.5, 40.8, 36.2, 32.5, 29.7, 22.7, 22.5, 22.4, 19.6, 18.1; IR (CH_2Cl_2) 3596 (br), 1747 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}O_3$ (M^+): 312.1725, found 312.1720; LRMS (EI, 20 eV) *m*/*z* 312 (M^+, 79), 297 (100). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.88; H, 7.75; Found C, 76.48; H, 7.76.

Preparation of (+)-34 and (+)-4. Followed the literature method.[5d]

(+)-34: 45% Yield, white solid, mp 174−175.5 °C (Et_2O/*n*-hexane) (lit.[5d] 180−181 °C); $[\alpha]^{20}_D$ = +31.2° (*c* 0.50, MeOH); analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f = 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 4.77 (m, 2H), 3.83 (s, 3H), 3.41 (sept, *J* = 6.9 Hz, 1H), 3.30−2.30 (m, 6H), 1.85 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.12 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 194.9, 173.3, 160.0, 158.4, 150.6, 142.2, 132.0, 125.8, 124.9, 118.8, 70.0, 62.7, 39.7, 37.8, 36.6, 32.0, 25.9, 23.7, 23.2, 21.5, 17.7; IR (CH_2Cl_2) 1755, 1678 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{24}O_4$ (M^+): 340.1675, found 340.1668; LRMS (EI, 20 EV) *m*/*z* 340 (M^+, 40), 325 (100).

(+)-4: 15% Yield, $[\alpha]^{20}_D$ = +110.1° (*c* 0.2, $CHCl_3$) [lit.[3c]: $[\alpha]^{20}_D$ = +110.3° (*c* 0.28, $CHCl_3$)]; UV λ^{MeOH}_{max} nm (log ϵ): 217 (4.18), 259 (4.10) [lit.[3c]: UV λ^{EtOH}_{max} nm (log ϵ): 219 (4.17), 260 (4.15)].

Preparation of (−)-35. Followed the procedure for (+)-**3**. 99% Yield, white solid, mp 174−175 °C (Et_2O/*n*-hexane) (lit.[5d] 175.5−176 °C); analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f = 0.57; $[\alpha]^{20}_D$ = −43.5° (*c* 0.17, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.05 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 4.77 (m, 2H), 3.35 (sept, *J* = 6.9 Hz, 1H), 3.19 (m, 1H), 2.84−1.70 (m, 6H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H),1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 173.2, 161.7, 159.6, 149.1, 136.0, 133.7, 126.1, 114.7, 113.6, 69.9, 40.3, 36.4, 31.6, 26.2, 25.3, 22.2, 22.1, 21.7, 17.8; IR (CH_2Cl_2) 3500 (br.), 1755, 1625 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}O_4$ (M^+): 326.1518, found 326.1518; LRMS (EI, 20 eV) *m*/*z* 326 (M^+, 57), 311(100).

Preparation of (+)-36. To a solution of (−)-**35** (0.321 g, 0.985 mmol) in methanol (11 mL) at 0 °C was added sodium borohydride (77.8 mg, 2.1 mmol) in three portions. The mixture was warmed to room temperature in a period of 2 h. Ice−water (10 mL) was added, followed by a saturated ammounium chloride solution (15 mL). The mixture was extracted with dichloromethane. The extracts were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (25% EtOAc in *n*-hexane) to give (+)-**36** (0.320 g, 99% yield) as a white solid, mp 125−127 °C (Et_2O/*n*-hexane) (lit.[5d] 127−128 °C); analytical TLC (silica gel 60), 40% EtOAc in *n*-hexane, R_f = 0.32; $[\alpha]^{20}_D$ = +53.5° (*c* 0.20, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 5.21 (m, 1H), 4.76 (m, 2H), 3.78 (br. d, *J* = 7.0 Hz, 1H), 3.30 (sept, *J* = 6.9 Hz, 1H), 2.78 (d, *J* = 13.3 Hz, 1H), 2.60−1.50 (m, 6H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 162.3, 154.3, 143.2, 133.9, 126.0, 125.5, 121.1, 115.5, 70.6, 69.0, 40.4, 36.5, 32.6, 30.3, 26.5, 23.1, 22.6, 22.5, 17.9; IR (CH_2Cl_2) 3581

(br.), 3360, 1753 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}O_4$ (M^+): 328.1675, found 328.1659; LRMS (EI, 20 eV) *m/z* 328 (M^+, 1), 310 (100), 295 (84).

Preparation of Mono-Epoxide (−)-37. To a solution of (+)-**36** (0.273 g, 0.832 mmol) in methanol (5.4 mL) at 0 °C was added a solution of $NaIO_4$ (195.6 mg, 0.914 mmol) in water (double distilled, 1.8 mL). The reaction flask was covered with aluminum foil. A yellow solution with white precipitate was formed. After stirred at room temperature for 1 h, the precipitate was filtered off and rinsed with dichloromethane. The filtrates were concentrated, and the residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford (−)-**37** (0.260 g, 96% yield) as a yellow solid, mp 82−83 °C (Et_2O/*n*-hexane) (lit.[5d] 80−83 °C); analytical TLC (silica gel 60), 35% EtOAc in *n*-hexane, $R_f = 0.25$; $[\alpha]^{20}_D = -327.5°$ (*c* 0.25, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, $J = 6.7$ Hz, 1H), 6.41 (d, $J = 6.7$ Hz, 1H), 4.69 (m, 2H), 4.07 (d, $J = 5.0$ Hz, 1H), 2.92 (m, $J = 6.9$ Hz, 1H), 2.60−1.50 (m, 7H), 1.15 (s, 3H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 173.3, 160.1, 150.3, 142.3, 135.1, 125.4, 121.0, 70.0, 66.7, 57.1, 43.6, 38.2, 32.8, 26.2, 24.2, 21.7, 21.4, 17.5, 16.9; IR (CH_2Cl_2) 1755, 1658 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, found 326.1520; LRMS (EI, 20 eV) *m/z* 326 (M^+, 97), 311 (96), 203 (100).

Preparation of (−)-38. To a solution of compound **37** (208 mg, 0.64 mmol) in acetonitrile (5 mL) was added an aqueous Na_2(EDTA) solution (4×10^{-4} M, 4.8 mL). The resulting homogeneous solution was cooled to 0−1 °C, followed by addition of 1,1,1-trifluoroacetone (0.2 mL) via a precooled syringe. To this homogeneous solution was added in portions a mixture of sodium bicarbonate (0.13 g, 1.55 mmol) and Oxone (0.308 g, 1.0 mmol) in a period of 1 h (pH 7−7.5). The reaction was monitored by TLC. The mixture was poured into water and extracted with dichloromethane. The extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (10−16% EtOAc in *n*-hexane) to afford (−)-**38** (153.2 mg, 70% yield) as a white solid, mp 219−220.5 °C (Et_2O/*n*-hexane) (lit.[5d] 218−219 °C); analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.18$; $[\alpha]^{20}_D = -267.2°$ (*c* 0.168, CH_3CN); ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dd, $J = 4.7$, 1.1 Hz, 1H), 4.70 (m, 2H), 3.82 (d, $J = 4.7$ Hz, 1H), 3.60 (d, $J = 5.3$ Hz, 1H), 2.85 (sept, $J = 6.9$ Hz, 1H), 2.80 (d, $J = 13$ Hz, 1H), 2.40−1.90 (m, 4H), 1.70 (m, 1H), 1.30 (m, 1H), 1.13 (s, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0, 159.6, 150.3, 136.6, 134.0, 126.0, 70.0, 62.1, 59.5, 54.7, 51.6, 41.0, 35.1, 30.2, 27.2, 23.5, 21.5, 21.4, 17.2, 13.7; IR (CH_2Cl_2) 1755, 1680 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}O_5$ (M^+): 342.1467, found 342.1464; LRMS (EI, 20 eV) *m/z* 342 (M^+, 47), 299 (87), 193 (86), 150 (100).

Preparation of (−)-Triptonide [(−)-2]. To a solution of (−)-**38** (56.8 mg, 0.166 mmol) in methanol (2 mL) at 0 °C was added a NaOH solution (1 N, 0.086 mL) followed by hydrogen peroxide (30%, 0.027 mL). After being stirred at room temperature for 1 h, the mixture was diluted with water and extracted with EtOAc. The extracts were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (45% EtOAc in *n*-hexane) to afford (−)-**2** (57.0 mg, 96% yield) as a white solid, mp 224−225 °C (Et_2O/*n*-hexane) (lit.[5d] 225−226 °C); analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.33$; $[\alpha]^{20}_D = -172.0°$ (*c* 0.064, CH_2Cl_2) [lit.[3a] −175° (*c* 0.148, CH_2Cl_2)]; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (m, 2H), 4.05 (d, $J = 3.0$ Hz, 1H), 3.83 (d, $J = 3.0$ Hz, 1H), 3.42 (d, $J = 5.3$ Hz, 1H), 2.90−1.20 (m, 8H), 1.08 (s, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 173.0, 159.4, 125.7, 69.9, 66.5, 65.1, 60.9, 60.4, 58.9, 56.0, 40.6, 35.3, 30.5, 25.8, 23.3, 18.0, 17.1, 16.3, 13.8; IR (CH_2Cl_2) 1762, 1724, 1681 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}O_6$ (M^+) 358.1416, found 358.1413; LRMS (EI, 20 eV) *m/z* 358 (M^+, 5), 329 (54), 297 (66), 287 (100).

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. We thank Dr. K.-K. Cheung for X-ray structural analysis and Prof. Y.-C. Li for providing an authentic sample of **2**.

Supporting Information Available: The preparation of compounds **25** and **26**; the 2D-COSY and NOESY spectra of compounds **D** and **E** as well as X-ray structural analysis of **D**; HPLC analysis of synthetic compound **5**; the CD spectra of compounds **2**, **4**, **5**, **25**, **26**, and **31**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9919613