Lanthanide Triflates Catalyze Mn(III)-Based Oxidative Radical Cyclization Reactions. Enantioselective Synthesis of (−)-Triptolide, (−)-Triptonide, and (+)-Triptophenolide

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

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

Received January 19, 1999

The $Mn(OAc)_3$-mediated oxidative free radical cyclization method has been successfully used for construction of polycyclic ring structures found in many natural products, especially terpenoids.[1] The excellent stereoselectivities, mild reaction conditions, and compatibility with a range of functional groups render the radical cyclization method an attractive alternative to the olefin-cation polycyclization method.[2] However, enantioselective radical cyclization remains a significant challenge.[3] Herein we report a highly enantioselective radical cyclization approach to (−)-triptolide (Figure 1), a potent antitumor and immunosuppressive agent isolated from the Chinese medicinal plant *Tripterygium wilfordii* Hook F (Lei Gong Teng).[4]

In our synthetic route to (±)-triptolide and its various analogues,[5] a $Mn(OAc)_3$-mediated radical cyclization reaction of compound **4a** or **4b** was employed to construct the tricyclic core (Scheme 1), providing trans product **5a** or **5b**, respectively, as the major isomer. On the basis of Snider's method,[3a] we used (−)-8-phenylmenthol as the chiral auxiliary, and obtained up to 9:1 diastereomer ratio of **8** and **9** for the radical cyclization of chiral β-keto ester **7** (Scheme 2). The oxidative radical cyclization reactions were proposed to proceed in at least three steps (Scheme 3).[6] $Mn(OAc)_3$ functions as a Lewis acid (LA) to promote enol formation and then as a single electron oxidant to generate the electrophilic radical, which subsequently adds to the C═C double bond. We conjectured that, when a stronger LA is used, the enol formation would be more favorable and the electrophilicity of the radical would be enhanced by chelation to the LA, thereby increasing the rates for radical cyclization reactions. Furthermore, recent studies reveal that LA may enhance the stereoselectivity of radical addition reactions.[7] Therefore, the effect of LA on the oxidative radical cyclization reactions was investigated.

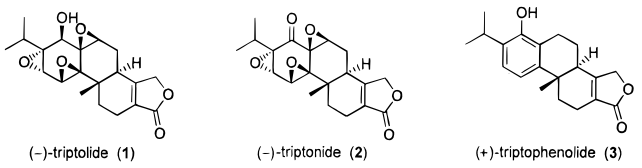
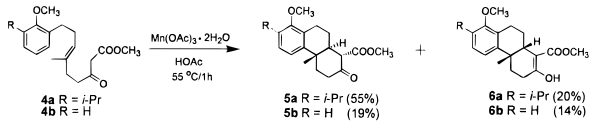
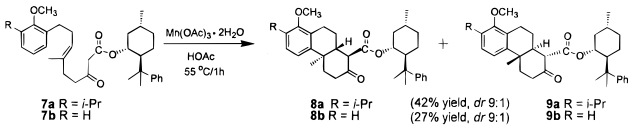


Figure 1.

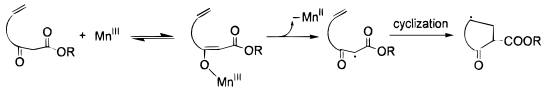
Scheme 1



Scheme 2



Scheme 3



Lanthanide triflates, $Ln(OTf)_3$, have been used as Lewis acid catalysts in protic solvents for a variety of reactions, such as Aldol condensations[8] and aza Diels−Alder reactions.[9] Thus, several lanthanide triflates were tested in the $Mn(OAc)_3$-mediated radical cyclization of achiral compounds **4a** and **4b** (Table 1). Without $Ln(OTf)_3$, cyclization reactions were very slow in HOAc at room temperature or in CF_3CH_2OH at 0 °C (entries 1−3). However, in the presence of ytterbium triflate, the reactions proceeded remarkably faster, providing higher yields as well as better stereoselectivities (entries 4−6). The reaction in CF_3CH_2OH at 0 °C appeared to be faster than that in HOAc at room temperature (entry 4 vs 5). Among the lanthanide triflates tested, $Yb(OTf)_3$ and $Er(OTf)_3$ were found to be better than others (entries 5−13). Most importantly, the use of a catalytic amount of $Ln(OTf)_3$ did not result in a significant decrease in yields (entry 7 vs 8). These results clearly indicate that *lanthanide triflates catalyze the Mn(OAc)$_3$-mediated radical cyclization reactions*.[10]

For radical cyclization of the (−)-8-phenylmenthyl ester **7a**, the syn and anti orientations of the two carbonyl groups may lead to opposite chiral induction based on the favorable chairlike transition states (Figure 2). In the syn orientation, the 8-phenyl group can effectively shield the (*si*)-face of the radical and restrict the cyclization to the (*re*)-face to give **8a**. In the anti orientation, however, only the (*si*)-face is accessible for the radical cyclization, providing diastereomer **9a**. As the bidentate chelation of β-keto esters to $Ln(OTf)_3$ would lock the two carbonyl groups in a syn orientation, we expect to obtain higher diastereoselectivity for

(1) (a) For a recent review on manganese(III)-based oxidative free radical cyclization reactions, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945. (c) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (d) Snider, B. B.; Dombroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487. (e) Snider, B. B.; Mohan, R. M.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841. (f) Zoretic, P. A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 4779. (g) Zoretic, P. A.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1162. (h) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z. *J. Org. Chem.* **1996**, *61*, 1806.

(2) (a) For a recent review on olefin-cation cyclization reactions, see: Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.9. For examples of asymmetric olefin-cation cyclization reactions, see: (b) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. (c) Corey, E. J.; Luo, G.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126, and references therein.

(3) (a) Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640. (b) Snider, B. B.; Wan, B. Y.-F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(4) (a) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194. (b) Kupchan, S. M.; Schubert, R. M. *Science* **1974**, *185*, 791.

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

(6) (a) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. (b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.

(7) (a) Guindon, Y.; Lavallee, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701. (b) Guindon, Y.; Guerin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528. (c) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (d) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (e) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063. (f) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190. (g) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (h) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274.

(8) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.

(9) Yu, L.-B.; Li, J.; Ramirez, J.; Chen, D.-P.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 903.

(10) Further investigation on the role of LA in these reactions is underway.

10.1021/ja9901664 CCC: $18.00
Published on Web 05/29/1999

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

entry	substrate	$Ln(OTf)_3$ (equiv)	solvent	reaction temp (°C)	reaction time (h)	yield (%)[b] **5**/**6**
1	**4a**	none	HOAc	rt	8−9	45/15
2	**4a**	none	CF_3CH_2OH	0	24	36/7
3	**4b**	none	CF_3CH_2OH	0 to rt	27	29/6
4[c]	**4a**	$Yb(OTf)_3 \cdot H_2O$ (1.0)	HOAc	rt	9	69/6
5[c]	**4a**	$Yb(OTf)_3 \cdot H_2O$ (1.0)	CF_3CH_2OH	0	3	69/10
6	**4b**	$Yb(OTf)_3 \cdot H_2O$ (0.3)	CF_3CH_2OH	0	3.5	59/8
7	**4a**	$Er(OTf)_3$ (1.0)	CF_3CH_2OH	0	2.5	73/2
8	**4a**	$Er(OTf)_3$ (0.2)	CF_3CH_2OH	0	6.5	67/7
9	**4b**	$Er(OTf)_3$ (0.2)	CF_3CH_2OH	0	6.5	62/9
10	**4a**	$Sm(OTf)_3$ (1.0)	CF_3CH_2OH	0	3	63/8
11	**4b**	$Sm(OTf)_3$ (0.2)	CF_3CH_2OH	0	6.5	44/10
12	**4a**	$Y(OTf)_3$ (1.0)	CF_3CH_2OH	0	5.5	57/7
13	**4a**	$Pr(OTf)_3$ (0.2)	CF_3CH_2OH	0	5	63/7

[a] All reactions were run in degassed solvent at 0.1 M concentration with 2.2 equiv of $Mn(OAc)_3 \cdot 2H_2O$. [b] Isolated yield. [c] Use of anhydrous $Yb(OTf)_3$ gave similar results.

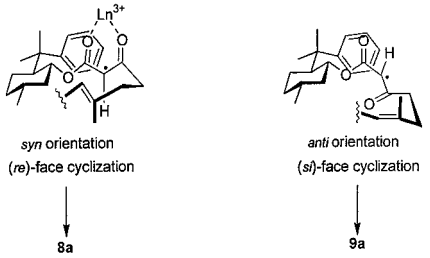
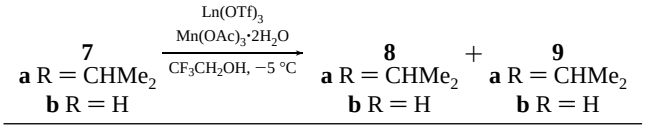


Figure 2.

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



7 **a** R = $CHMe_2$, **b** R = H → **8** **a** R = $CHMe_2$, **b** R = H + **9** **a** R = $CHMe_2$, **b** R = H

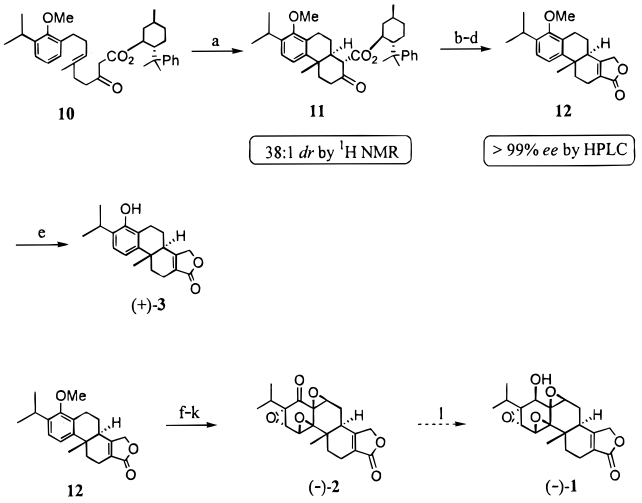
entry	substrate	$Ln(OTf)_3$ (equiv)	yield[b] (%)	diastereomer ratio[c] **8**:**9**
1	**7a**	$Yb(OTf)_3 \cdot H_2O$ (1)	77	38:1
2	**7a**	$Yb(OTf)_3 \cdot H_2O$ (0.2)	71	26:1
3	**7b**	$Yb(OTf)_3 \cdot H_2O$ (0.2)	66	36:1
4	**7a**	$Sm(OTf)_3$ (0.2)	73	28:1
5	**7a**	$Pr(OTf)_3$ (0.2)	76	24:1
6	**7a**	$Eu(OTf)_3$ (0.2)	68	26:1
7	**7b**	$Er(OTf)_3$ (0.2)	67	27:1

[a] All reactions were carried out in degassed CF_3CH_2OH at 0.05 M concentration with 2.2 eq. of $Mn(OAc)_3 \cdot 2H_2O$ at −5 °C. [b] Isolated yield. [c] The ratios were determined by ^1H NMR analysis (500 MHz, $CDCl_3$) of the crude product (for details see Supporting Information).

8a when lanthanide triflates are used as catalysts. Indeed, in the presence of $Yb(OTf)_3$ (1.0 equiv), the cyclization of **7a** afforded 77% of trans products **8a** and **9a** (ratio 38:1) and a trace amount of cis isomer (the configuration of which is unknown) (Table 2, entry 1). Both the yield and diastereoselectivity were higher compared to the case without $Ln(OTf)_3$ (Scheme 2). Similar diastereoselectivities (ratios higher than 24:1) were obtained when 20 mol % of lanthanide triflates were employed in the cyclization reactions of **7a** and **7b** (Table 2, entries 2−7). The excellent chiral induction suggests the importance of LA in controlling the carbonyl rotamer population in the cyclization step.[7]

Oxidative radical cyclization of the (+)-8-phenylmenthyl ester **10** in the presence of $Yb(OTf)_3$ afforded major diastereomer **11** (dr 38:1), which was ultimately transformed into (+)-triptophenolide (**3**)[11] and (−)-triptonide (**2**)[4b] (Scheme 4).[5] In view of the prior work on the conversion of (±)-triptonide into (±)-triptolide,[5,12] a formal enantioselective synthesis of (−)-triptolide (**1**) was thus accomplished.

Scheme 4[a]



[a] Reagents and conditions: (a) $Mn(OAc)_3 \cdot 2H_2O$ (2.2 equiv), $Yb(OTf)_3 \cdot H_2O$ (1.0 equiv), CF_3CH_2OH, −5 °C, 77%; (b) KHMDS, THF, −78 °C to −30 °C, then $PhNTf_2$, 95%; (c) DIBAL−H (2.2 equiv), CH_2Cl_2, −78 to −30 °C, 20 h, 63%; (d) CO, Bu_3N, $Pd(Ph_3P)_4$, LiCl, CH_3CN, 65 °C, 12 h, 93%; (e) BBr_3, CH_2Cl_2, −78 °C to rt, 98%; (f) CrO_3, HOAc (aq), rt, 45%; (g) BBr_3, CH_2Cl_2, −78 °C to rt, 99%; (h) $NaBH_4$, MeOH, 0 °C, 2 h, 99%; (i) $NaIO_4$, MeOH/H_2O (3:1), 0 to 25 °C, 96%; (j) CF_3COCH_3, oxone, $NaHCO_3$, CH_3CN/H_2O (3:2), 0 °C, 70%; (k) H_2O_2, NaOH, MeOH, 25 °C, 96%; (l) see ref 5.

We expect that our highly enantioselective radical cyclization methodology should have tremendous potential in asymmetric synthesis of many polycyclic natural products. In addition, our study opens up the possibility of using chiral Lewis acids for catalytic asymmetric radical cyclization reactions.[13]

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council.

Supporting Information Available: Experimental details for the radical cyclization reactions, preparation of **7a** and **7b**, determination of diastereomeric ratio of **8** and **9**, and synthesis of **2** and **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9901664

(11) (a) Deng, F.-X.; Zhou, B.-N.; Song, G.-Q.; Hu, C.-Q. *Acta Pharm. Sin.* **1982**, *17*, 146. (b) Wu, D.-G.; Sun, X.-C.; Li, F. *Acta Bot. Yunnanica* **1979**, *1*, 29.

(12) Buckanin, R. S.; Chen, S. J.; Frieze, D. M.; Sher, F. T.; Berchtold, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 1200.

(13) (a) Wu, J. H.; Radinov, R.; Porter, N. A.*J. Am. Chem. Soc.* **1995**, *117*, 11029. (b) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (c) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (d) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713.