Investigation of Mn(III)-Based Oxidative Free Radical Cyclization Reactions toward the Synthesis of Triptolide: The Effects of Lanthanide Triflates and Substituents on Stereoselectivity

Dan Yang,* Xiang-Yang Ye, Ming Xu, Kwan-Wah Pang, and Kung-Kai Cheung

Contribution from the Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

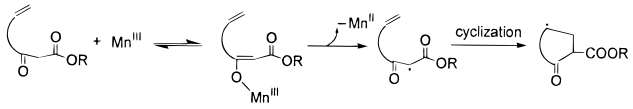
Received October 6, 1999

Abstract: Mn(III)-mediated oxidative free radical cyclization reactions are useful for construction of polycyclic compounds. In the total synthesis of triptolide (**3**) and its related compounds, construction of tricyclic skeletons **4** and **5** was achieved by the $Mn(OAc)_3$-mediated oxidative radical cyclization of a series of acyclic precursors **6**−**9**. The addition of a catalytic amount of lanthanide triflates was found to significantly improve the rate and stereoselectivity of those radical cyclization reactions. The effects of the benzylic oxygen substituents and α-substituents (chloro and methyl) on the radical cyclization reactions were also investigated. Transition-state models were proposed to explain the observed stereoselectivity.

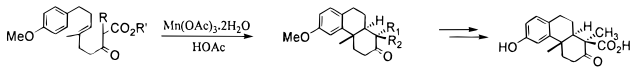
Introduction

Mn(III)-mediated oxidative free radical cyclization reactions are an important class of reactions for organic synthesis.[1,2] The oxidative free radical cylization reactions of unsaturated β-keto esters were proposed to proceed in at least three steps (Scheme 1).[2,3] $Mn(OAc)_3$ promotes enol formation and then functions as a single-electron oxidant to generate the electrophilic radical, which subsequently adds to the C=C double bond. These reactions allow formation of multiple C−C bonds with excellent stereoselectivities, mild reaction conditions, and compatibility with a range of functional groups. As an attractive alternative to the olefin-cation polycyclization method,[4] the oxidative radical cyclization method has been successfully applied to the construction of monocyclic, bicyclic, tricyclic, and tetracyclic compounds.[5] For examples, Snider et al. used cyclization of β-keto ester **1** to obtain tricyclic compound **2**, the key intermediate for the synthesis of podocarpic acid (Scheme 2).[6]

Scheme 1



Scheme 2



1a R = H, R' = Me
1b R = Me, R' = Et

2a $R_1 = CO_2Me$, R_2 = H (70%)
2b R_1 = Me, $R_2 = CO_2Et$ (50%)

Podocarpic acid

In our total synthesis of triptolide (**3**)[7] and its related compounds, construction of tricyclic skeletons **4** and **5** was achieved by the $Mn(OAc)_3$-mediated oxidative radical cyclization of a series of acyclic precursors **6**−**9** (Chart 1). We found that lanthanide triflates have significant effects on the rate and stereoselectivity of those radical cyclization reactions. We also investigated the effects of the benzylic oxygen substituents and α-substituents (chloro and methyl) on the radical cyclization reactions. The results are disclosed herein. A portion of the work was published earlier.[8]

Results and Discussion

Oxidative Radical Cyclization Reactions in the Absence of Lewis Acids. Acyclic precursors **6**−**9** were designed for the Mn(III)-based radical cyclization reactions (Chart 1). Compounds **6** and **7** possess oxygen substituents at the benzylic position, whereas **8** and **9** have none. Compounds **6b** and **9** contain an α-substituent (chloro or methyl) in the β-keto ester portion. The above precursors were synthesized by dianion displacement[6b,9] with various allylic bromides **A**−**D** (Scheme 3).

(1) (a) Bush, J. B., Jr.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903. (b) Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 5905. (c) Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977 (d) Corey, E. J.; Kang, M-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384.

(2) For an excellent recent review on manganese(III)-based oxidative free radical cyclizations, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(3) (a) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137 and references therein. (b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607. (c) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759.

(4) For reviews on olefin cation cyclization reactions, see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, part B, p 341. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.9, p 341.

(5) For examples, see: (a) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945. (b) Snider, B. B.; Dombroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487. (c) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (d) Zoretic, P. A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 4779. (e) Zoretic, P. A.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1162. (f) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z. *J. Org. Chem.* **1996**, *61*, 1806. (g) Zoretic, P. A.; Chen, Z.; Zhang, Y.; Ribeiro, A. A. *Tetrahedron Lett.* **1996**, *37*, 7909. (h) Jones, P.; Pattenden, G. *Synlett* **1997**, 398.

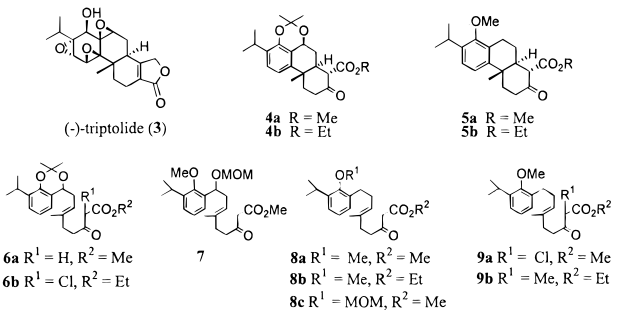
(6) (a) Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Zhang, Q.-W.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.

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

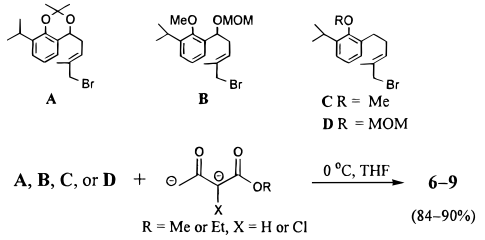
(8) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579.

10.1021/ja993598n CCC: $19.00
Published on Web 02/15/2000

Chart 1



Scheme 3



The radical cyclization reactions of compounds **6**−**9** were carried out in acetic acid with 2.1 equiv of $Mn(OAc)_3 \cdot 2H_2O$ either at 50 °C or at room temperature. The results are summarized in Table 1.

Effect of Oxygen Substituent at the Benzylic Position. Radical cyclization of substrates **6a** and **7**, both bearing oxygen substituents at the benzylic position, gave 40% yield for the *trans*-ring junction products and 8% yield for the *cis*-ring junction products at 50 °C (entries 1 and 3), but no reaction took place at room temperature (entries 2 and 4). In comparison, for the radical cyclization of **8a**−**c** that have no benzylic substituent, both the reaction rate and the yield were increased (entries 5−7). It seems that substitution at the benzylic position has a deleterious effect on the rate and yield of the radical cyclization reactions, probably due to the increased tendency for hydrogen abstraction at the benzylic position. This is corroborated by the fact that the benzylic oxidation products **21** and **22** were isolated respectively from the radical cyclization of **6a** in MeOH and **6b** under condition B (Scheme 4). Compound **22** was further converted to its 2,4-DNP derivative **23**.[10] The structures of **21** and **23** were determined by X-ray analysis.

The stereochemistries of cyclization products **4a**, **10**, **11**, and **12** were determined by using 2D-COSY and NOESY, and the structures of **4a** and **10** were further confirmed by X-ray structural analysis. Interestingly, the oxygen substituents at the benzylic position of *trans*-ring junction products **4a** and **11** have completely different orientations, that is, the acetonide group *cis* to the angular methyl group whereas the OMOM group *trans* to it. The observed high stereoselectivities could be explained using chairlike transition-state models shown in Figure 1. For the cyclization of **6a**, the acetonide group prefers the pseudoequatorial position due to ring constraint, affording the cyclization product **4a** with the benzylic oxygen in the β-orientation (TS1). However, the OMOM group at the benzylic position of **7** prefers the pseudoaxial orientation in order to avoid the steric interaction with the methoxy group on the phenyl ring (TS2). Molecular mechanics calculations using the Macromodel v4.5 program[11] were carried out to account for the observed stereoselectivity. The minimum global energies for the *trans*-ring junction products with different configurations at the benzylic position were calculated. The acetonide protected compound **4a** was found to be more stable than its benzylic α-epimer by 1.32 kcal mol^{-1}, and the MOM-protected compound **11** was found to be more stable than its benzylic β-epimer by 1.36 kcal mol^{-1}, consistent with our experimental result. The formation of compounds **4a** and **11** demonstrated the high stereoselectivity of the radical cyclization reactions as four stereo centers were set up in one step.

In Snider's case (Scheme 2), the cyclization reactions took place at room temperature, and only the *trans* products were found.[6a] Surprisingly, we obtained both *trans*- and *cis*-ring junction products at 50 °C for radical cyclization of **6**−**8** (Table 1, entries 1, 3, and 5−7). For substrates **8a**−**c**, the *cis* products were isolated in up to 20% yield, and the *trans*/*cis* ratio was only 5.5:2 as compared to the ratio of 5:1 for entries 1 and 3. The isolation of *cis* products suggests that the cyclization of those α-unsubstituted β-keto esters (**6a** and **7**−**8**) might not go through the concerted process which leads to the formation of the *trans* products (Figure 2). Instead, a two-step process may proceed. The intermediate radical (or cation) **E** adopts a chairlike conformation.[12] Further cyclization of this radical (or cation) may occur in both the axial and the equatorial directions, which gives the *cis* and the *trans* products, respectively.

Effect of α-Substituent. α-Chloro Substituent. According to the literature,[13] the presence of an α-chloro group can prevent the overoxidation of the β-keto esters and increase the yield. We found that, in the presence of α-chloro group, the substrates **6b** and **9a** were more reactive and the cyclization reactions could be carried out at room temperature (entries 8 and 9). The cyclization products **16**−**19** all have the *trans* configuration for the ring junction, with the ester group of the major diastereomers **16** and **18** in the axial position (*cis* to the angular methyl group), whereas that of the minor isomers **17** and **19** in the equatorial position (*trans* to the angular methyl group). The structures of **16**, **18**, and **19** were determined by X-ray analysis. The fact that no *cis*-ring junction product was found suggests that in the presence of α-chloro group the radical cyclization reaction is fast enough and proceeds through a concerted pathway. Subsequent dechlorination of compounds **16**/**17** and **18**/**19** with zinc in acetic acid[14] afforded the tricyclic products **5a** (99% yield) and **4b** (88% yield), respectively. Although one more step is required, the overall yield of **5a** is higher compared with the direct cyclization of **8a** (entry 5).

The stronger preference for the ester group in the axial position than for the chloro group is surprising given that the ester group in the axial position of a cyclohexane is less favorable than the chloro group due to larger 1,3-diaxial repulsion.[15] However, ab initio calculation using Gaussian 94 program[16]

(9) (a) Axelrod, E. H.; Milne, G. M.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139. (b) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(10) Behforouz, M.; Bolan, J. L.; Flynt, M. S. *J. Org. Chem.* **1985**, *50*, 1186.

(11) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

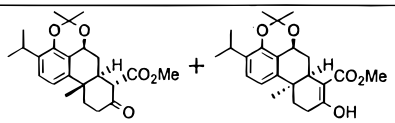
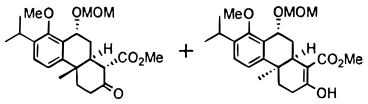
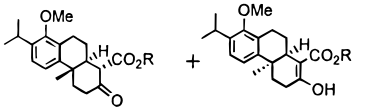
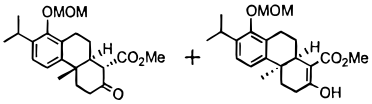
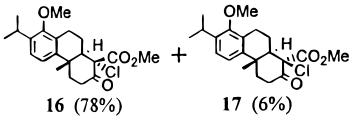
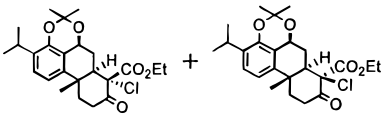
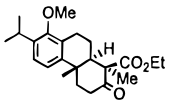
(12) Jensen, F. R.; Gale, L. H.; Rodgers, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 5793.

(13) (a) Snider, B. B.; McCarthy, B. A. *Tetrahedron* **1993**, *49*, 9447. (b) Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y.-S.; Kim, Y. K.; Yun, M.; Kim, S. *J. Am. Chem. Soc.* **1997**, *119*, 8391.

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

(15) In the cyclohexane system, the conformational energies $-\Delta G°$ (or *A* values) for Cl group and $COOCH_3$ group are 0.53−0.64 kcal mol^{-1} and 1.2−1.3 kcal mol^{-1}, respectively. See: Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 11, pp 695−697.

Table 1. Mn(III)-Based Oxidative Free Radical Cyclization of **6**−**9**[a]

entry	substrates	reaction conditions[b]	products (yield)[c]
1	**6a**	A	 **4a** (40%) **10** (8%)
2	**6a**	B	No reaction observed
3	**7**	A	 **11** (40%) **12** (8%)
4	**7**	B	No reaction observed
5	**8a**/**8b**	A	 **5a** R = Me (55%) **13a** R = Me (20%) **5b** R = Et (52%) **13b** R = Et (20%)
6[d]	**8a**	B	**5a** (45%) + **13a** (15%)
7	**8c**	A	 **14** (55%) **15** (20%)
8	**9a**	B	 **16** (78%) **17** (6%)
9	**6b**	B	 **18** (55%) **19** (6%)
10[e]	**9b**	B	 **20** (64%)

[a] All reactions were carried out in degassed acetic acid with 2.2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ at 0.1 M of the substrate concentration. [b] Condition A: 50 °C, 1 h; condition B: room temperature, 4−6 h. [c] Isolated yield. [d] The reaction time was 8−9 h with 80% conversion. [e] The reaction time was 8 h.

indeed suggested a slightly stronger preference for the axial CO_2CH_3 group than for the axial Cl group (Figure 3).

The ^{1}H NMR spectra revealed higher percentages of enol forms present in **6b** (30%) and **9a** (21%) than those in **6a** (5%) and **8a** (5%), respectively, due to the electron negativity of the α-chloro group. The relative reactivity of **6a** vs **6b** and **8a** vs **9a** might correlate with the percentage of the enol forms present at equilibrium.[3a] Furthermore, the electron-withdrawing chloro group makes the α-radical more electrophilic, and thus the addition of this radical to the C=C bond is also accelerated.

α-Methyl Substituent. The cyclization reaction of compound **9b** was carried out at room temperature in HOAc, affording *trans*-ring junction product **20** as a single isomer in 64% yield (Table 1, entry 10). No *cis*-ring junction product was isolated. Comparing entry 10 with entries 5 and 6, we find that the presence of α-methyl substituent also accelerates the radical cyclization reactions.[6] X-ray structural analysis of compound **20** revealed the axial orientation of the ester group. This can be explained using transition-state models shown in Figure 4. There are two transition states for the cyclization reaction, one having the ester group in the axial position and the other having the ester group in the equatorial position. It is more favorable to

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Peterson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Oriz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J. Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision A.1; Gaussian, Inc.: Pittsburgh, PA, 1995.

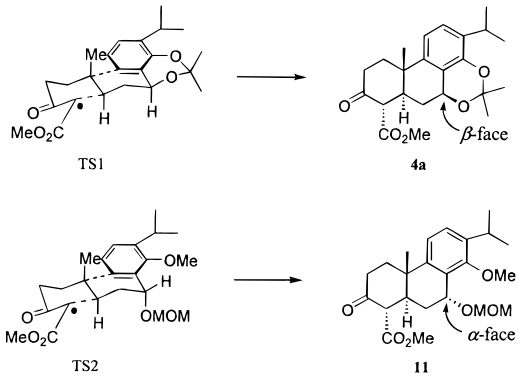
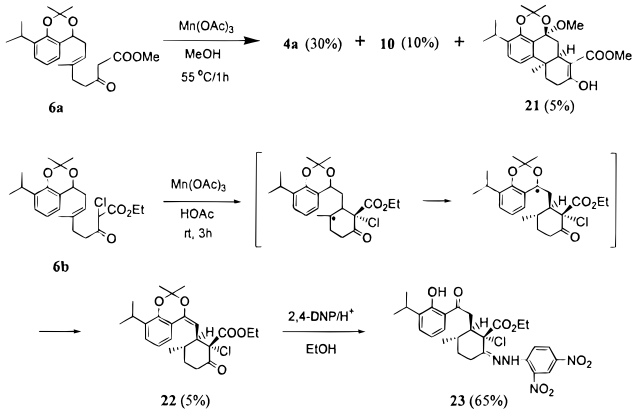


Figure 1.

Scheme 4



have the ester group in the axial position than it is for the methyl group because the ester group has less 1,3-diaxial repulsion with the angular methyl group.[17] As a result, compound **20** was obtained as the major cyclization product. This is in agreement with the selectivity observed by Snider and co-workers for the cyclization of **1b** (Scheme 2).[6]

Oxidative Radical Cyclization Reactions in the Presence of Lewis Acids. According to the proposed mechanism for the Mn(III)-mediated oxidative radical cyclization reactions (Scheme 1),[3] one of the functions of $Mn(OAc)_3$ is to act as a Lewis acid to promote the enol formation. We conjectured that, when a stronger Lewis acid is used, the enol formation would be more favorable and the electrophilicity of the radical would be enhanced by chelation to the Lewis acid, thereby increasing the rates for radical cyclization reactions. In fact, recent studies reveal that Lewis acids can accelerate some radical reactions, including radical addition and atom-transfer reactions, and can enhance the stereoselectivity of those reactions.[18] Therefore, the effect of Lewis acids on the oxidative radical cyclization reactions was investigated.

Lanthanide triflates, $Ln(OTf)_3$, have been used as Lewis acid catalysts in protic solvents for a variety of reactions, such as Aldol condensation reactions, Michael reactions, Friedel−Crafts acylations, and Diels−Alder reactions.[19] Thus, a series of lanthanide triflates were tested in the $Mn(OAc)_3$-mediated radical cyclization of compound **8a** (Table 2).

In the absence of lanthanide triflates, the radical cyclization reaction of **8a** was very slow at room temperature in HOAc, and some starting material remained even after 20 h (Table 2, entry 1). In the presence of 1.0 equiv of $Yb(OTf)_3 \cdot H_2O$, the radical cyclization reaction of **8a** was complete in 9 h with the *trans* and *cis* products isolated in 69 and 6% yields, respectively (entry 2). Apparently, the reaction was faster and the *trans*/*cis* ratio was improved from 2.2:1 to 11:1.

We then examined the solvent effect. The reaction in DMSO was slow at room temperature even with 1.0 equiv of $Yb(OTf)_3$ (Table 2, entry 3). In methanol, the reaction was very slow in the absence of $Ln(OTf)_3$ (entry 4). With the addition of $Yb(OTf)_3$ (1 equiv), the reaction in methanol proceeded much faster (entry 5), but the yield was not satisfactory. In MeOH or HOAc/MeOH mixed solvents at 0 °C, the radical cyclization resulted in low yields even in the presence of $Yb(OTf)_3$ (entries 6−8). Using CF_3CH_2OH as the solvent, the reaction at 0 °C was very slow in the absence of $Yb(OTf)_3$ (entry 9). However, with 1.0 equiv of $Yb(OTf)_3$, the reaction was complete in 3 h, and the *trans* product was isolated in 69% yield together with 10% of the *cis* product (entry 10). Therefore, CF_3CH_2OH was found to be a suitable solvent for the radical cyclization of compound **8a**, with satisfactory rate and yield.

Besides $Yb(OTf)_3$, more than 10 lanthanide triflates were evaluated in the Mn(III)-based radical cyclization of **8a** (Table 2, entries 10−22). Among them, $Yb(OTf)_3$ and $Er(OTf)_3$ are more effective Lewis acids than others in promoting the radical cyclization (entries 10 and 13). In addition, the use of a catalytic amount of lanthanide triflates did not decrease the yields significantly (entries 10 vs 11, 13 vs 14, and entry 18). These results clearly indicate that lanthanide triflates catalyze the Mn(III)-based radical cyclization reactions.

To elucidate the effect of lanthanide triflates, ^1H NMR studies on the enol formation of ethyl acetoacetate in the presence and in the absence of $Yb(OTf)_3$ were carried out (Table 3). The results revealed that, in the presence of $Yb(OTf)_3$, the percentage of the enol form was significantly increased. It seems possible that the $Yb(OTf)_3$ accelerates the radical cyclization through the increase of enol population. Furthermore, with the chelation by $Yb(OTf)_3$, the α-radical may become more electrophilic (Figure 5), and the addition of this radical to C═C bond may also be accelerated, hence increasing the reaction rate and the *trans*/*cis* ratio.

We also examined the effect of lanthanide triflates on the radical cyclization of compounds **6a**, **6b**, **9a**, and **9b**. We found that, in the presence of $Yb(OTf)_3$, substrates **6a**, **6b**, and **9a** bearing the benzylic acetonide-protecting group or the α-chloro group decomposed quickly (Table 4, entries 1−3). For the α-methyl-substituted substrate **9b** (entry 4), the radical cyclization reaction carried out at 0 °C in the absence of $Yb(OTf)_3$ was not complete in 8 h (74% conversion), and two diastereomers **20** and **24** were isolated in 26% and 5% yields, respectively. The predominant formation of **20** is a result of the steric effect in the transition states as shown in Figure 4. In contrast, the cyclization of **9b** in the presence of 1 equiv of $Yb(OTf)_3$ proceeded faster as the starting material disappeared in 8 h (entry 5). The *trans*-ring junction products **20** and **24** were isolated in 7 and 18% yields, respectively, along with a side product **25** (31% yield).

(17) In the cyclohexane system, the 1,3-diaxial interaction (expressed as free energy difference $-\Delta G°$) for CH_3/CH_3 groups and CH_3/COOEt groups are 3.7, and 2.8−3.2 kcal mol^{-1}, respectively. See: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 11, pp 706−707.

(18) For a recent review of Lewis acids in free radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(19) (a) For the review of $Ln(OTf)_3$ as Lewis acid catalysts in organic synthesis, see: Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. (c) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, 6815. (d) Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1157. (e) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett.* **1994**, 545. (f) Yu, L.-B.; Li, J.; Ramirez, J.; Chen, D.-P.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 903.

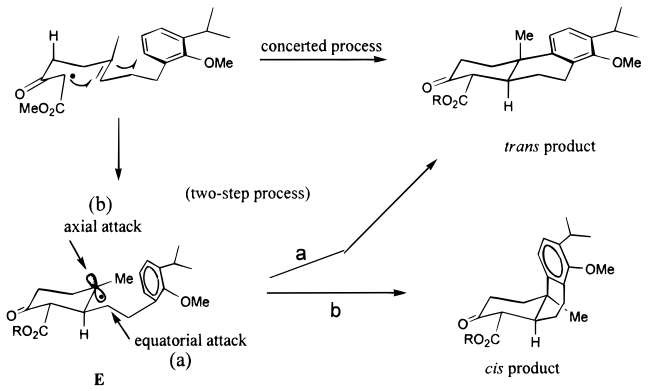


Figure 2.

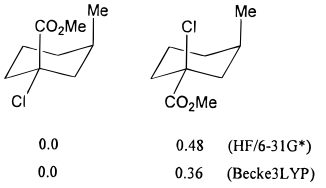


Figure 3.

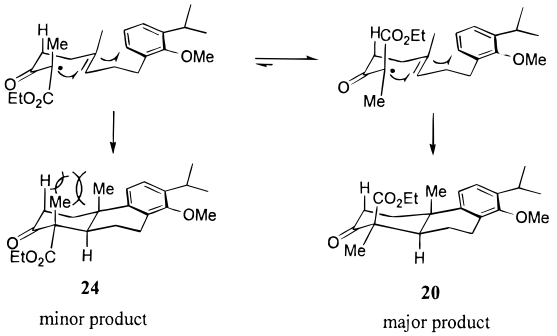


Figure 4.

Note that, in the presence of $Yb(OTf)_3$, the ratio of **20**/**24** was reversed (5.2:1 for entry 4, and 1:2.6 for entry 5). We explain this result using the $Yb(OTf)_3$ chelation model (Scheme 5). $Yb(OTf)_3$ can bind to the β-keto ester **9b** and lock the two carbonyl groups in a *syn* orientation, thereby accelerating the radical cyclization process and affording **24 (**the thermodynamically less stable isomer) as the major product. The side product **25** was also formed as a result of the chelation of $Yb(OTf)_3$ to the two carbonyl groups (Scheme 5). In this case, the first C−C bond was formed significantly faster than the second one, and the radical intermediate **F** was further oxidized by Mn^{3+} to cation **G**, which was then trapped intramolecularly by the ester group to form **25**.

In summary, lanthanide triflates can catalyze the Mn(III)-based oxidative radical cyclization reactions of β-keto esters with or without α-substituents. For the latter class of substrates, excellent stereoselectivities and yields have been obtained.

Conclusions

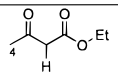
An efficient and stereoselective $Mn(OAc)_3$-mediated oxidative free radical cyclization method has been developed, which utilizes lanthanide triflates as Lewis acid catalysts. This method should have many applications in synthesis of polycyclic natural products. In fact, compounds **4**, **5**, **14**, and **16** have recently been demonstrated as key intermediates in synthesis of triptolide (**3**) and its various analogues in our efforts on developing new antiinflammatory and immunosuppressive agents.[7] In addition, our study opens up the possibility of using chiral Lewis acids to catalyze the enantioselective Mn(III)-based free radical cyclization reactions.[20] Work in that direction is in progress.

Table 2. $Ln(OTf)_3$-Promoted Oxidative Free-Radical Cyclization of **8a** Mediated by $Mn(OAc)_3 \cdot 2H_2O$[a]

entry	$Ln(OTf)_3$ (equiv)	solvent	reaction temp (°C)	reaction time (h)	yield (%)[b] **5a**/**13a**
1	none	HOAc	rt	9	45/15
2	$Yb(OTf)_3 \cdot H_2O$ (1.0)	HOAc	rt	9	69/6
3	$Yb(OTf)_3 \cdot H_2O$ (1.0)	DMSO	rt	24	NA[c]
4	none	MeOH	rt	24	NA[c]
5	$Yb(OTf)_3 \cdot H_2O$ (1.0)	MeOH	rt	10	30/trace
6	$Yb(OTf)_3 \cdot H_2O$ (1.0)	MeOH	0	17	26/trace
7	$Yb(OTf)_3 \cdot H_2O$ (1.0)	HOAc/MeOH (9:1)	0	24	NA[c]
8	$Yb(OTf)_3 \cdot H_2O$ (1.0)	HOAc/MeOH (8:2)	0	24	NA[c]
9	none	CF_3CH_2OH	0	24	36/7
10[d]	$Yb(OTf)_3 \cdot H_2O$ (1.0)	CF_3CH_2OH	0	3	69/10
11	$Yb(OTf)_3 \cdot H_2O$ (0.3)	CF_3CH_2OH	0	3.5	59/8
12	$Eu(OTf)_3$ (1.0)	CF_3CH_2OH	0	2	52/14
13	$Er(OTf)_3$ (1.0)	CF_3CH_2OH	0	2.5	73/2
14	$Er(OTf)_3$ (0.2)	CF_3CH_2OH	0	6.5	67/7
15	$Sm(OTf)_3$ (1.0)	CF_3CH_2OH	0	3	63/8
16	$Tb(OTf)_3$ (1.0)	CF_3CH_2OH	0	2.5	53/9
17	$Y(OTf)_3$ (1.0)	CF_3CH_2OH	0	3.5	57/7
18	$Pr(OTf)_3$ (0.2)	CF_3CH_2OH	0	5	63/7
19	$La(OTf)_3$ (1.0)	CF_3CH_2OH	0	2	39/13
20	$Tm(OTf)_3$ (1.0)	CF_3CH_2OH	0	2.5	29/6
21	$Dy(OTf)_3$ (1.0)	CF_3CH_2OH	0	2.5	33/14
22	$Gd(OTf)_3$ (1.0)	CF_3CH_2OH	0	2	21/3

[a] All reactions were carried out at 0.1 M concentration in the degassed solvent with 2.2 equiv of $Mn(OAc)_3 \cdot 2H_2O$. [b] Isolated yield. [c] The reaction was very slow. No attempt was made to isolate the products. [d] Use of anhydrous $Yb(OTf)_3$ gave similar result.

Table 3. NMR Studies on the Enol Population of Ethyl Acetoacetate[a]

substrate	percentage of enol form (%)[b]		
	$Yb(OTf)_3$ (0 eq.)	$Yb(OTf)_3$ (0.5 eq.)	$Yb(OTf)_3$ (1.0 eq.)
	18.1	66.9	72.0

[a] The ^1H NMR spectra (300 MHz) were recorded in CD_3OD. [b] The percentage of enol form was calculated by the integration of the C-4 methyl signals.

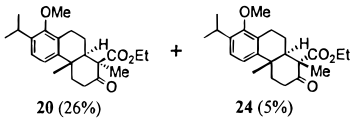
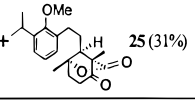
Experimental Section

Typical Procedure for the Radical Cyclization in the Absence of Lanthanide Triflates. To a solution of **8c** (376 mg, 1.0 mmol) in degassed acetic acid (10 mL) was added $Mn(OAc)_3 \cdot 2H_2O$ (590 mg, 2.2 mmol). The mixture was stirred at 50 °C for 1 h. A solution of $NaHSO_3$ (10%) was added to quench the reaction. The mixture was extracted with CH_2Cl_2. The extracts were dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography to afford compound **14** (205.7 mg, 55% yield) and **15** (74.8 mg, 20% yield).

Typical Procedure for the Radical cyclization in the Presence of Lanthanide Triflates. To a solution of acyclic precursor **8a** (346 mg, 1.0 mmol) in degassed CF_3CH_2OH (10 mL) was added $Yb(OTf)_3 \cdot H_2O$ (620 mg, 1.0 mmol) under argon atmosphere. The mixture was stirred at room temperature for 10 min, then cooled to 0 °C. $Mn(OAc)_3 \cdot 2H_2O$ (590 mg, 2.2 mmol) was added in one portion. The reaction was monitored by TLC. Saturated $NaHSO_3$ solution was added to the

(20) (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1990**, *23*, 163. (b) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029. (c) Sibi, M. P.; Ji, J. Wu, J. H.; Gurtler, S.; Porter, N. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (d) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702.

Table 4. Effect of Lanthanide Triflates on the Mn(III)-Based Radical Cyclization of α-Substituted Acyclic Precursors[a]

entry	substrate	$Yb(OTf)_3$ (eq.)	reaction time (h)	products (yields)[b]
1	**6a**	1.0	1	–[d]
2	**6b**	1.0	1	–[d]
3	**9a**	1.0	1	–[d]
4	**9b**[c]	none	8	 **20** (26%) + **24** (5%)
5	**9b**	1.0	8	**20** (7%) + **24** (18%) +  **25** (31%)

[a] All of the reactions were carried out in degassed CF_3CH_2OH (0.1 M concentration) at 0 °C with 2.1 equiv of $Mn(OAc)_3 \cdot 2H_2O$. [b] Isolated yields. [c] 74% conversion. [d] Starting material decomposed.

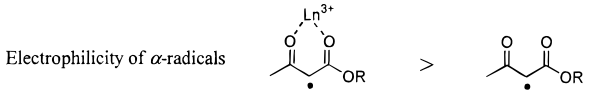


Figure 5.

mixture which was then extracted with dichloromethane. The extracts were dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (8 to 16% EtOAc in *n*-hexane) to afford **5a** (237 mg, 69% yield) and **13a** (34 mg, 10% yield).

Acknowledgment. This work was supported by the University of Hong Kong and the Hong Kong Research Grants Council. We thank Mr. Man-Fai Ng for performing the ab initio calculation.

Supporting Information Available: Experimental details for the preparation of acyclic precursors **6**−**9**; characterization data for compounds **5b**, **11**, **12**, **13b**, and **14**−**25**; 2D-COSY and 2D-NOESY spectra for compounds **16** and **17**; X-ray structural analysis for compounds **16**, **18**−**21**, **23**, and **24** (print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA993598N

Scheme 5