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Et_2AlCl-Promoted Asymmetric Phenylseleno Group Transfer Radical Cyclization Reactions of Unsaturated β-Hydroxy Esters

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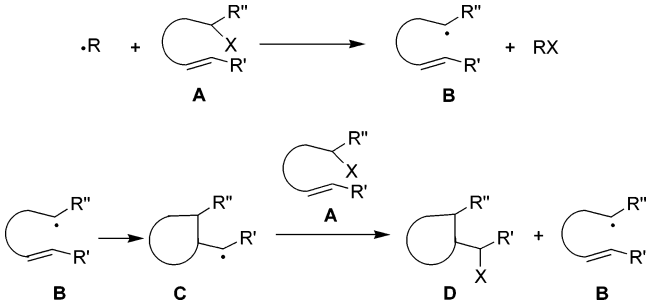
We have developed a new method for asymmetric phenylseleno group transfer radical cyclization of unsaturated β-hydroxy esters. Various unsaturated α-phenylseleno β-hydroxy esters underwent radical cyclization in the presence of Et_2AlCl in benzene with sunlamp irradiation at 25−30 °C to give mono- and bicyclic group-transferred products in an efficient and highly regioselective and diastereoselective manner. To rationalize the high diastereoselectivities observed in this reaction, we propose a model based on chelation control of the aluminum alkoxides that are formed in situ. We devised a general method to prepare chiral radical precursors from which we obtained highly optically pure mono- and bicyclic group transfer products. The synthetic advantages of this method are demonstrated by our formal total synthesis of (−)-wilforonide. This paper presents the first examples of stereoselective group transfer radical cyclizations that occur via 1,2-asymmetric induction.

Introduction

Since the pioneering work of Curran, atom or group transfer radical cyclization has become an important method for the synthesis of cyclic compounds.[1,2] Scheme 1 outlines the general mechanism for atom or group transfer radical cyclization reaction. Once generated, radical **B** undergoes radical cyclization to form the cyclic radical **C**. Following abstraction of an X group from another substrate **A**, the radical is terminated to give the desired product **D**. The transferred group can be a halogen atom (X = Cl, Br, or I) or a phenyl chalcogen group (X = SePh or TePh).[2c] Because the reactive X group, suitable for further chemical transformations, remains in the product after the cyclization reaction, the whole process provides an attractive alternative to the traditional reductive radical cyclization methods, in which the radicals are usually terminated by abstraction of a hydrogen atom.

It is well-documented in the literature that Lewis acids can be applied to radical reactions to obtain higher reactivities and/or stereoselectivities.[3] Although exciting

SCHEME 1



developments have been achieved in chiral Lewis acid-mediated enantioselective radical reactions,[4] diastereoselective radical reactions with chiral auxiliary approaches,[5] and 1,2-asymmetric inductions[6] (radicals bearing an adjacent chiral center), *the use of Lewis acids in atom or group transfer radical reactions is far from common, particularly in the preparation of chiral cyclic compounds.*[4f,6i,7] Recently, we reported the first enantioselective atom transfer radical cyclization reaction that is catalyzed by chiral Lewis acids.[8] The cyclization of

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(2) For reviews, see: (a) Jasperese, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237−1286. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, Chapter 1.5. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, Chapter 4.2.

(3) For recent review on the use of Lewis acids in free radical reactions, see: Guérin, B.; Ogilvie, W. W.; Guindon, Y. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, Chapter 4.4.

(4) For recent reviews, see: (a) Sibi, M. P.; Rheault, T. R. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 461. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171. (c) Curran, D. P.; Porter, N. A.; Giese, B., Eds. *Stereochemistry of Radical Reactions*: *Concepts*, *Guidelines*, *and Synthetic Applications*; VCH: Weinheim, Germany, 1996. (d) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*; Pergamon: Oxford, UK, 1996; Vol. 14. (e) Renaud, P.; Gerster, M. *Angew. Chem*., *Int. Ed.* **1998**, *37*, 2563−2579. (f) Sibi, M. P.; Manyem, S.; Zimmerman J. *Chem. Rev.* **2003**, *103*, 3263−3295.

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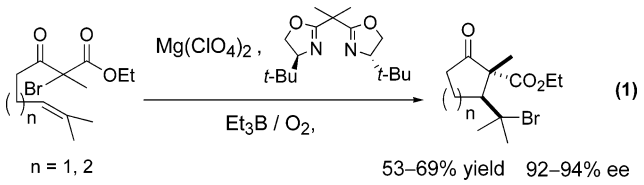
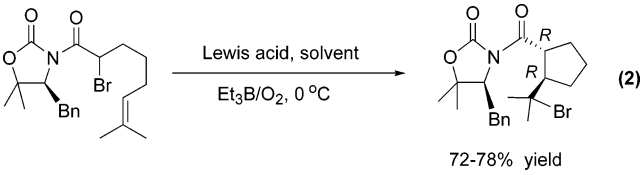
unsaturated α-bromo *β*-keto esters catalyzed by a chiral $Mg(ClO_4)_2$/bis(oxazoline) complex resulted in ee values of up to 94% for the cyclization product (eq 1). For those

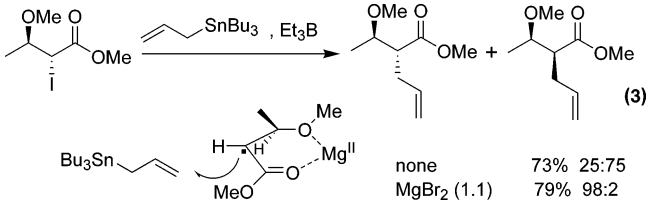


reactions, the presence of an α-alkyl group in the substrates is essential: the corresponding α-bromo *β*-keto esters lacking the α-methyl group were unstable and difficult to purify[9] and their cyclization reactions occurred with poor enantioselectivities. We also reported the chiral auxiliary-controlled, Lewis acid-catalyzed highly asymmetric atom transfer radical cyclization reactions of unsaturated α-bromo oxazolidinone imides (eq 2).[10] Al-

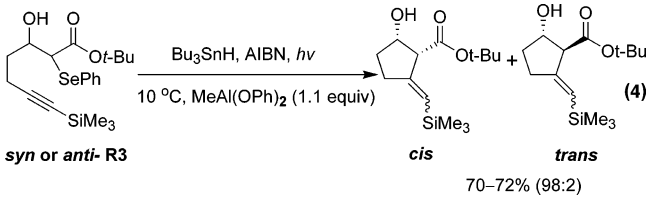


though excellent diastereoselectivities could be achieved, this approach requires the introduction and removal of chiral auxiliaries. We believe that a more general and efficient method to access chiral atom or group transferred cyclic compounds still requires exploration.

Guindon's group was the first to report the Lewis acid-controlled 1,2-asymmetric induction radical reaction;[6c] since then, a number of exciting results have been achieved from the extensive studies undertaken by the research groups of Guindon and Renaud with respect to the following types of radical reactions: allylation,[6c,i,j] reduction,[6k] addition,[6l] and reductive cyclization.[11] For example, Guindon's group reported that the stereochemical outcome of the α-allylation reaction of 3-methoxy-2-iodobutyate was completely reversed when the radical reaction was conducted in the presence of $MgBr_2$. The reversal of diastereoselectivity was attributed to the chelation between $MgBr_2$ and the *β*-alkoxy ester moiety of the radical intermediate (eq 3).[6c]



Recently, Renaud and co-workers reported an aluminum oxide-controlled *tributyltin hydride reductive* radical cyclization reaction (eq 4).[11] Through chelation control from the aluminum oxide formed in situ, high diastereoselectivities were observed in the radical addition to the TMS-substituted electron-rich triple bonds under reductive radical conditions. The authors also presented the first example of a cascade radical reaction controlled by a Lewis acid under similar conditions.



We envisioned that the application of 1,2-asymmetric induction in atom or group transfer radical cyclization reactions would provide an efficient method to synthesize multifunctionalized chiral cyclic compounds and would overcome the shortages of our previous methods. In practical terms, we sought to find Lewis acids and radical initiation conditions for reactions that would meet the following criteria: (1) They should allow group transfer radical cyclization reactions that provide more synthetically useful and terminally functionalized cyclic products. At the same time, the procedure must eliminate the need to use toxic tributyltin hydride. (2) The procedure should be general in allowing the cyclization of readily available simple and less-electron-rich alkenes, and to provide

(5) For a recent review, see: (a) Porter, N. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, Chapter 4.3. For selected recent examples, see: (b) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190–192. (c) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421–422. (d) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274–275. (e) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090–6091. (f) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779–10780. (g) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155–5160. (h) Mero, C. L.; Porter, N. A. *J. Org. Chem.* **2000**, *65*, 775–781. (i) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873–8879.

(6) (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845–2848. (b) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27–30. (c) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912–4914. (d) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166–1178. (e) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, E.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288–289. (f) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701–9702. (g) Guindon, Y.; Guérin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Synlett* **1995**, 449–451. (h) Guindon, Y.; Guérin, B.; Rancourt, J.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Pure Appl. Chem.* **1996**, *68*, 89. (i) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528–12535. (j) Gerster, M.; Audergon, L.; Moufid, N.; Renaud, P. *Tetrahedron Lett.* **1996**, *37*, 6335–6338. (k) Rancourt, J.; Guindon, Y. *J. Org. Chem.* **1998**, *63*, 6554–6565. (*l*) Urabe, H.; Yamashita, K.; Sunuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576–3577. (m) Nagano, H.; Kuno, Y.; Omori, Y.; Iguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 389–394. (n) Nagano, H.; Kuno, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 987–988.

(7) (a) Mero, C. L.; Porter, N. A. *J. Org. Chem.* **2000**, *65*, 775–781. (b) Clark, A. J.; Campo, F. D.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastecoueres, D.; Thomas, G. H.; Verlhac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671–680. (c) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 922–927. (d) Fang, X.; Xia, H.; Yu, H.; Dong, X.; Chen, M.; Wang, Q.; Tao, F.; Li, C. *J. Org. Chem.* **2002**, *67*, 8481–8488. (e) Feng, H.; Kavrakova, I. K.; Pratt, D. A.; Tellinghuisen, J.; Porter, N. A. *J. Org. Chem.*, **2002**, *67* 6050–6054.

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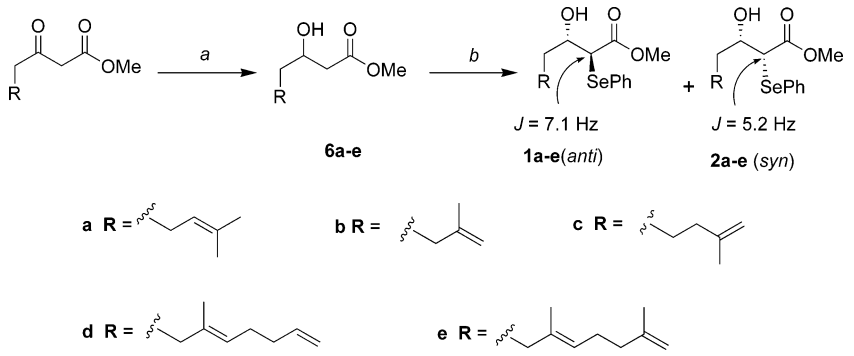
(9) Yan, Y.-L. Ph.D. Thesis, The University of Hong Kong, 2003.

(10) Yang, D.; Zheng, B.-F.; Gu, S.; Chan, W. H. P.; Zhu, N.-Y. *Tetrahedron: Asymmetry* **2003**, *14*, 2927–2937.

(11) Renaud, P.; Andrau, L.; Schenk, K. *Synlett* **1999**, 1462–1464.

SCHEME 2[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 5 min, 85−90%; (b) LDA (2 equiv), THF, −35 °C, then PhSeBr, −78 °C, 70−80% (**1**:**2** = 10:1).

carbocyclic compounds having various ring sizes and substituents. (3) A simple, but practical, method to gain access to chiral radical precursors should be developed so that optically pure cyclic products can be obtained.

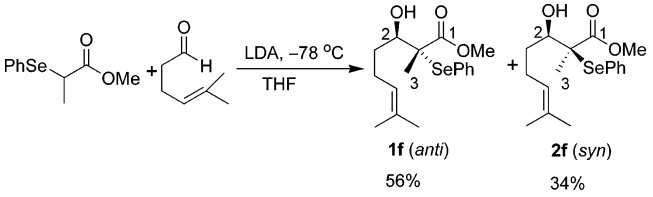
In this paper, we report a new method that addresses all of the considerations above. We have discovered an Et_2AlCl-promoted asymmetric PhSe group transfer radical cyclization reaction of unsaturated β-hydroxy esters and have applied it successfully to tandem cyclization reactions for the construction of various optically pure bicyclic skeletons.

Results and Discussion

Preparation of Precursors for Radical Cyclization Reactions. The preparation of α-phenylseleno-β-hydroxy esters **1** and **2** is presented in Scheme 2. β-Keto esters having various olefinic side chains were reduced with $NaBH_4$ to afford the corresponding β-hydroxy esters **6** in good yield. These β-hydroxy esters were treated with 2 equiv of LDA to generate the corresponding dianions, and the latter were phenylselenated with PhSeBr in a highly diastereoselective manner to afford **1** (anti) and **2** (syn) in a 10:1 ratio.[12] The relative configurations of **1** and **2** were determined by comparing the ^{1}H NMR spectroscopic coupling constants between the α and β protons with those of a literature report.[13b] Isomers *anti*-**1** usually have larger *J* values (>7 Hz) than those of *syn*-**2** (5.2 Hz). When compared with the literature procedure for preparing similar α-phenylseleno compounds, which involves Lewis acid-promoted aldol condensation,[13] the dianion approach is more efficient and results in higher anti-selectivity.

Compounds **1f** and **2f**, which each bear an α-methyl substituent, were synthesized by the aldol condensation between methyl-α-(phenylseleno)propionate[14] and 5-methylhex-4-enal (Scheme 3). The relative configurations of these two compounds were determined by comparing their ^{13}C NMR spectroscopic data with those of known

SCHEME 3



compounds.[15] The signals of the C1 (174.54 ppm), C2 (74.68 ppm), and C3 (18.12 ppm) nuclei in **1f** are all relatively downfield of those of the C1 (173.65 ppm), C2 (72.67 ppm), and C3 (17.21 ppm) nuclei in **2f**.[16]

Optimization of Reaction Conditions. We optimized the reaction conditions for the radical cyclization of unactivated olefinic β-hydroxy ester **1a** by investigating different Lewis acids, solvents, temperatures, and initiating methods; Table 1 summarizes the results. Almost no reaction took place in the absence of Lewis acids, due to the low electrophilicity of the α-centered radical intermediate (entry 1). Lewis acids such as $Mg(ClO_4)_2$, $Zn(OTf)_2$, and $Ti(Oi\text{-}Pr)_2Cl_2$ were inefficient at promoting the cyclization reactions at 0 °C when using either Et_3B/O_2 or UV light to initiate the radical formation; only 5−10% of the substrates were consumed (entries 2−4). A similar result was obtained in the presence of Me_3Al (entry 5).[11] When Et_2AlCl was used in the Et_3B/O_2-initiated radical reaction, we obtained a good yield (65%) of the cyclization products (entry 6), but **3a**, **4a**, and **5a** were obtained as a mixture in a ratio of 1:4.2:4.8. The formation of the side product **5a** might be the result of disproportionation of the tertiary radical intermediate after the cyclization. To suppress the formation of **5a**, we considered other radical initiation methods. A remarkable amount of **5a** (25%) was obtained even when AIBN/*hv* was used to initiate the radical reaction, although the total yield was improved to 78% (entry 7). We found that a simple photolysis using a 300-W sunlamp at 25−30 °C overcame this problem (entry 8): a highly stereoselective cyclization took place to give **3a** and **4a** in a 10:1 ratio in 77% yield; the formation of **5a** was suppressed completely. When the solvent was changed to toluene, cyclization products **3a**, **4a**, and **5a** were

(12) For a study on the stereoselective α-alkylation of β-hydroxy esters, see: Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269−1277.

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(14) Yamashita, T.; Yasuda, M.; Watanabe, M.; Kojima, R.; Tanabe, K.; Shima, K. *J. Org. Chem.* **1996**, *61*, 6438−6441.

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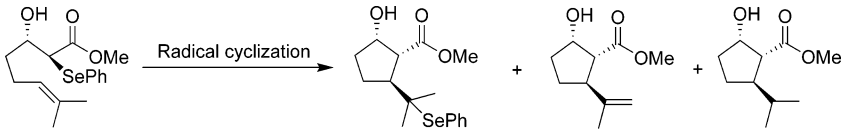
(16) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294−4299.

TABLE 1. Effects of Lewis Acids and Initiating Conditions on the Diastereoselective Phenylseleno Group Transfer Radical Cyclization Reaction of 1a[a]



1a 3a 4a 5a

entry	Lewis acid (equiv)	solvent	temp, °C	initiating condition	time, h	yield, %[b] (**3a**:**4a**:**5a**)
1		CH_2Cl_2	0	Et_3B/O_2	12	<5
2	$Mg(ClO_4)_2$ (1.1)	CH_2Cl_2	0	Et_3B/O_2 or *hv*	6	<5
3	$Zn(OTf)_2$ (1.1)	toluene	0	Et_3B/O_2 or *hv*	20	<5
4	$Ti(Oi\text{-}Pr)_2Cl_2$ (1.1)	toluene	0	Et_3B/O_2	4.5	<5
5	Me_3Al (2)	toluene	0	Et_3B/O_2	4.5	<5
6	Et_2AlCl (2)	toluene	0	Et_3B/O_2	4.5	65 (1:4.2:4.8)
7	Et_2AlCl (2)	toluene	rt	AIBN/*hv*	9	78 (3:2.8:2)
8	Et_2AlCl (2)	benzene	rt	sunlamp[c]	7.5	77 (10:1:0)
9	Et_2AlCl (2)	toluene	rt	sunlamp[c]	14	80 (20:1:1)
10	Et_2AlCl (2)	benzene	rt		2	

[a] All reactions were conducted with 0.3−0.6 mmol of **1a** in the indicated solvent (30 mL/mmol). [b] Isolated yield. [c] A 300-W sunlamp was used.

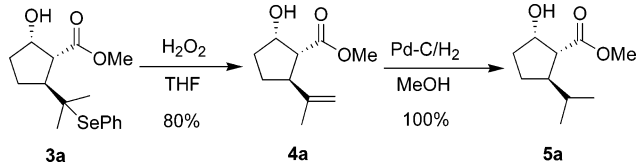
formed in a 20:1:1 ratio in 80% yield (entry 9). No reaction was observed in the absence of radical initiation (entry 10), which indicates the radical nature of the mechanism of this cyclization reaction.

Et_2AlCl plays a critical role in enhancing the yield of this reaction. When treated with Et_2AlCl, the radical precursor forms an aluminum alkoxide quantitatively.[6l,17b] For the addition of α-centered radicals toward unactivated olefins under such mild conditions (sunlamp/25−30 °C), higher cyclization rates should be obtained for α-centered radicals that are more electron deficient. Although its Lewis acidity decreased as a result of the formation of the aluminum alkoxide, EtAlClOR is still strong enough to cause the α-centered radical to become more electrophilic and, thus, the cyclization rate is accelerated. In addition, the PhSe group transfer process may be faster in the presence of the Lewis acid.[7f] The other Lewis acids, such as Me_3Al,[11] probably also complex with the *β*-hydroxy ester moieties, but their Lewis acidities are not high enough to promote the radical addition. We did not examine stronger Lewis acids, such as BF_3 or $TiCl_4$, because previous studies have suggested the possible decomposition of unsaturated α-phenylseleno ketones in the presence of strong Lewis acids.[17a] We added 2 equiv of Et_2AlCl to compensate for any Lewis acid that might be hydrolyzed by traces of moisture. Because oxygen also destroys this Lewis acid, it is very important to degas the reaction system with argon before adding Et_2AlCl.

We confirmed the structure of **3a** by X-ray crystallographic analysis.[18] The oxidative elimination of the phenylseleno group of **3a** with H_2O_2 provided an olefinic product, which we confirmed spectroscopically to be **4a**. Hydrogenation of **4a** gave product **5a** (Scheme 4).

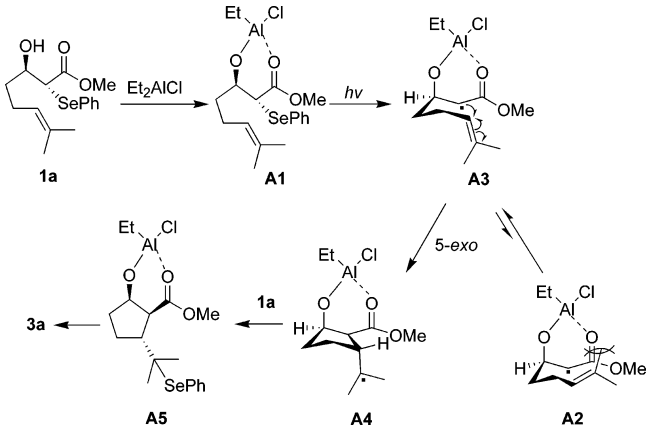
In Scheme 5 we propose a chelation control mechanism to explain the high diastereoselectivity observed in the radical cyclization reactions.[11] Upon reaction with the Lewis acid (Et_2AlCl), **1a** forms the alkoxyaluminum

SCHEME 4



3a 4a 5a

SCHEME 5



complex **A1** in which the ester carbonyl group is complexed with the aluminum center. Once the radical is generated by photolysis, the olefinic group can approach the radical center only via transition state **A2** or **A3**. Transition state **A2** is less favorable, however, because of the steric interactions between the pseudoaxial olefinic Me group and the chelating ring. The 5-exo attack on the alkene group via transition state **A3** results in the five-membered-ring radical intermediate **A4**. Subsequent group transfer would be accomplished when radical **A4** abstracts the phenylseleno group from another substrate molecule to give the cyclization product **3a**.

Next, we examined the reactions of various unsaturated α-phenylseleno *β*-hydroxy ester substrates under our optimized radical cyclization conditions (Table 2). These results demonstrate that excellent regio- and diastereoselectivities can be achieved for the Et_2AlCl-promoted phenylseleno group transfer radical cyclization

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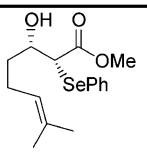
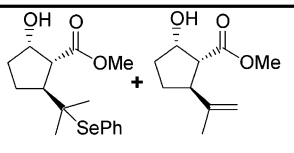
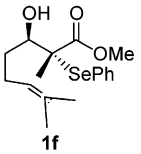
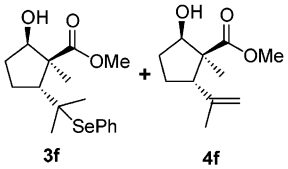
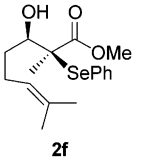
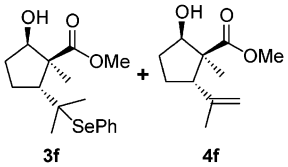
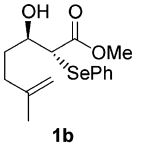
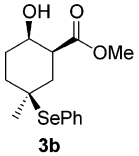
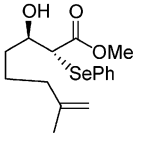
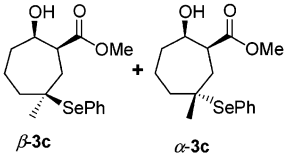
(18) See the Supporting Information.

TABLE 2. Et_2AlCl-Promoted Phenylseleno Group Transfer Monocyclization Reactions[a]

entry	substrate	time	product	yield[b]
1	 **2a**	10 h	 **3a** + **4a**	71% (**3a**:**4a** = 6:1)
2	 **1f**	7.5 h	 **3f** + **4f**	79% (**3f**:**4f** = 3:1)[c]
3	 **2f**	7.5 h	 **3f** + **4f**	78% (**3f**:**4f** = 3:1)
4	 **1b**	7.5 h	 **3b**	77%
5	 **1c**	5.4 h	 *β*-**3c** + *α*-**3c**	56% (*β*:*α* = 3:4)[d]

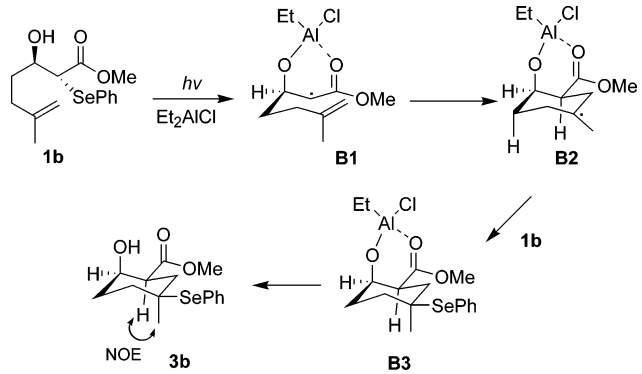
[a] Reaction conditions: 2 equiv of Et_2AlCl, 300-W sunlamp, 25−30 °C, 0.3−0.6 mmol of substrate in benzene (30 mL/mmol). [b] Isolated yield.

reactions. Cyclization of the syn-isomer **2a** gave exclusively the cis, trans products **3a** and **4a** as a 6:1 mixture in 71% yield (entry 1). When comparing this reaction with the cyclization of the anti radical precursor **1a**, it is obvious that the cis, trans cyclic products were formed preferentially and independent of the stereochemistry of the radical precursors. We then tested if this substrate independence could be applied to α-methyl α-phenylseleno *β*-hydroxy ester substrates **1f** and **2f**. Indeed, we obtained similar results. Both the radical precursors, *anti*-**1f** and *syn*-**2f**, gave only the cis, trans cyclization products **3f** and **4f** in the same ratio (3:1) and in good yields (79% and 78%, respectively; entries 2 and 3). These observations indicate that the radical cyclizations of **1f** and **2f** proceeded through the same radical intermediate.

For the reaction of the *β*-hydroxy ester **1b**, we isolated the desired 6-endo product **3b** as the only cyclization product in 77% yield (entry 4). A strong NOE observed between the α-H and methyl protons provides evidence to suggest that the methyl group resides in an axial position. The α-centered radical attacks the disubstituted olefin predominately from the less-hindered side (Scheme 6). After cyclization, radical **B2** abstracts the phenylseleno group of **1b** from the *β*-face to give the product **B3**. The approach of **1b** from the α-face is apparently hindered by the two axial hydrogen atoms.

For the cyclization of **1c**, the α-centered radical attacks the less-substituted side of the alkene to form exclusively the 7-endo cyclization products **3c** as a pair of epimers

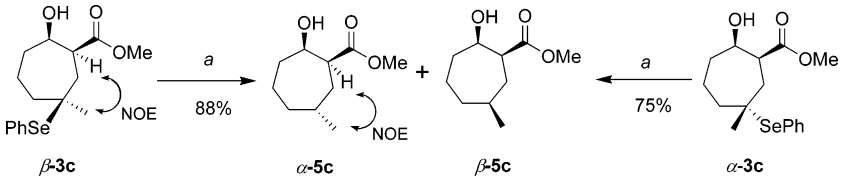
SCHEME 6



(*β*:α = 3:4; entry 4). To determine the stereochemistries of α-**3c** and *β*-**3c**, both isomers were treated independently with *n*-$Bu_3SnH/Et_3B/O_2$ in benzene at room temperature; reduction products **5c** were obtained as a pair of epimers in the same ratio (α:*β* = 4:3; Scheme 7). The stereochemistries of *β*-**3c** and α-**5c** were established by the use of 2D NOESY experiments (see the Supporting Information).

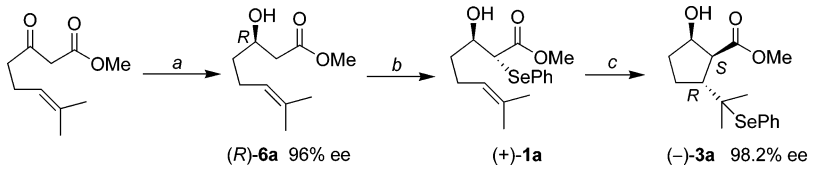
Preparation of Optically Pure Radical Precursors and Their Applications in Tandem Radical Cyclization Reactions. Multifunctional chiral cyclic compounds are useful building blocks for the synthesis of natural products. We expected that an extension of the group transfer radical reactions described above to chiral

SCHEME 7[a]



[a] Reagents and conditions: (a) Bu_3SnH, Et_3B/O_2, benzene, rt.

SCHEME 8[a]



[a] Reagents and conditions: (a) H_2, 1 atm, $RuBr_2$[(*R*)-Binap] (3%), 50 °C, 99%, 96% ee; (b) LDA, THF, −35 °C, then PhSeBr, −78 °C, 70%; (c) Et_2AlCl, benzene, sunlamp, 25 °C, 77%, 98.2% ee.

precursors would make these cyclization reactions more attractive and practical for the enantioselective synthesis of natural products.

Chiral radical precursors can be obtained readily by phenylselenation of optically pure β-hydroxy esters according to Scheme 2. Chiral β-hydroxy esters are usually prepared by asymmetric reduction of β-keto esters[19,20] as well as by kinetic enzymatic resolution of β-hydroxy esters.[21] Chiral β-hydroxy ester (*R*)-**6a** was prepared readily from the corresponding β-keto ester in quantitative yield and 96% ee following Genet's protocol (Scheme 8),[19f] under which the trisubstituted olefin was not reduced. Chiral radical precursor (+)-**1a** was prepared from (*R*)-**6a** following the same procedure as that described in Scheme 2. Radical cyclization of (+)-**1a** under our optimized reaction condition (entry 8, Table 1) provided (−)-**3a**, which contains three adjacent chiral centers, in up to 98% ee. We determined the absolute configuration of (−)-**3a** by X-ray crystallographic structural analysis.[18]

Previously, we demonstrated the advantages that phenylseleno groups have in group transfer tandem radical cyclization reactions.[22] The transferred group is suitable for further chemical transformations.[2] Tandem radical cyclizations, in which two or more carbon−carbon bonds are formed in successive steps in one reaction without the isolation of reaction intermediates, are regarded as economically favorable synthetic methods.[23] Therefore, atom or group transfer tandem radical cyclizations that combine the advantages of the two types of reactions should be simple, highly efficient, and useful synthetic processes. By applying our monocyclization method to chiral diene substrates, we expected to obtain various synthetically useful, bicyclic phenylseleno group transfer products that contain multiple chiral centers.

Unfortunately, we found that asymmetric hydrogenation of β-keto esters was inefficient when they bear terminal olefinic groups (Scheme 9). Under Genet's conditions,[19d−f] the terminal olefin units always reduced faster than did the keto groups to give products that were a mixture of **7d** and **8d**. To prepare chiral unsaturated β-hydroxy esters, we converted the β-keto ester into its potassium salt **9d** and attempted a bakers' yeast reduction of this salt; we abandoned this approach because of the poor yield and the tedious workup procedure.[24]

(19) For examples of the asymmetric hydrogenation of β-keto esters, see: (a) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372. (b) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134−9135. (c) Burk, M. J.; Harper, G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423−4424. (d) Genet, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Cano de Andrade, M. C.; Lafitte, J. A. *Tetrahedron*: *Asymmetry* **1994**, *5*, 665−674. (e) Genet, J. P.; Ratovelomanana-Vidal, V.; Cano de Andrade, C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36,* 4801−4804. (f) Greck, C.; Ferreira, F.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031−2034.

(20) For reviews on the reduction of β-keto esters with bakers' yeast, see: (a) Davies, F. H. G.; Green, R. H.; Kelly, D. R.; Roberts, S. M. *Biotransformations in Preparative Organic Chemistry. The Use of Isolated Enzymes and Whole Cell Systems in Synthesis*; Academic Press: London, UK, 1989; Chapter 3. (b) Servi, S. *Synthesis* **1990**, 1−25. (c) Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49−97. (d) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071−1140. (e) D'Arrigo, P.; Pedrocchi Fantoni, G.; Servi, S.; Strini, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2375−2379.

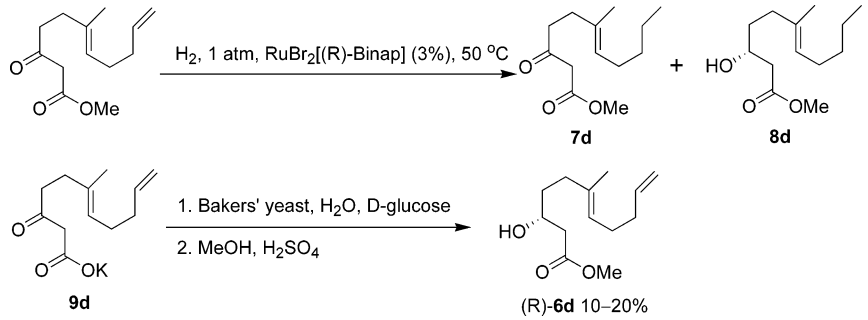
(21) (a) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5241−5244. (b) Itoh, T.; Kuroda, K.; Tomosada, M.; Takagi, Y. *J. Org. Chem.* **1991**, *56*, 797−804.

(22) Yang, D.; Gao, Q.; Lee, O.-Y. *Org. Lett.* **2002**, *4*, 1239−1241.

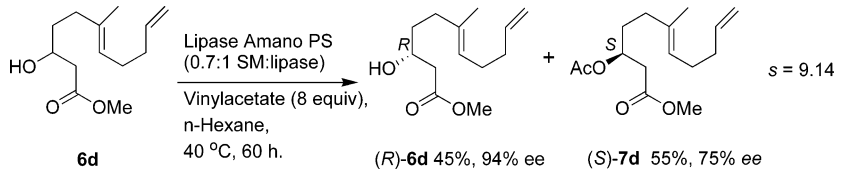
(23) For recent reviews on tandem radical cyclization reactions, see: (a) Malacria, M. *Chem. Rev*. **1996**, *96*, 289−306. (b) McCarroll, A. J.; Walton, J. C. *Angew. Chem.*, *Int. Ed.* **2001**, *40*, 2224. (c) Snider, B. B. *Chem. Rev*. **1996**, *96*, 339−363. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. For recent examples, see: (e) Curran, D. P.; Sisko, J.; Balog, A.; Sonoda, N.; Nagahara, K.; Ryu, I. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, *10*, 1591−1953. (f) Kim, S.; Cheong, J. H.; Yoo, J. *Synlett* **1998**, 981−982. (g) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579−5580. (h) Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J. A.; Hursthouse, M. B.; Hibbs, D. *J. Org. Chem*. **1999**, *64*, 7856−7862. (i) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc*. **1999**, *121*, 9875−9876. (j) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599−3601. (k) Hiton, S. T.; Jones, K.; Tim, C. T.; Pljevaljcic, G.; Schulte, M. *Chem. Commun*. **2001**, 209−210. (*l*) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717−4727. (m) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett*. **2001**, *3*, 2435−2438. (n) Haruo, Y.; Hasegawa, T.; Tanaka, H.; Takahashi, T. *Synlett* **2001**, 1935−1937. (o) Zhou, S.; Bommezijn, S.; Murphy, J. A. *Org. Lett.* **2002**, *4*, 443−445.

(24) (a) Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1988**, *53*, 860−863. (b) Hirama, M.; Shimizu, M.; Iwasjita, M. *J. Chem, Soc.*, *Chem. Commun.* **1983**, 559−600.

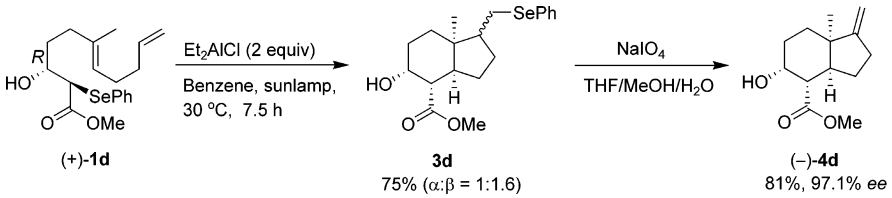
SCHEME 9



SCHEME 10



SCHEME 11

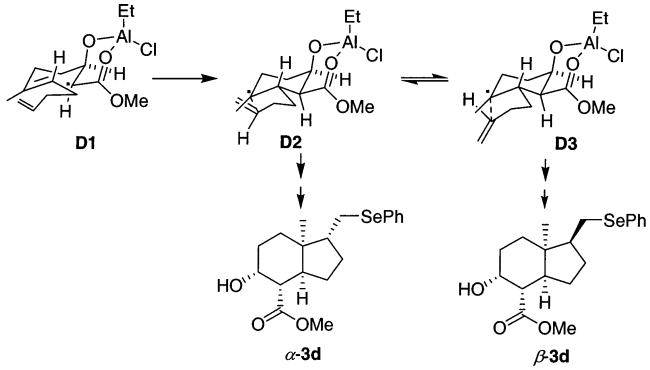


Finally, we found that the application of lipase Amano PS, which has been used in the resolution of saturated β-hydroxy esters,[25] was a better choice for effecting the resolution. We obtained the chiral β-hydroxy ester (R)-**6d** readily in 45% yield and 94% ee when using this enzyme-catalyzed transesterification method (Amano PS/vinyl acetate/*n*-hexane; Scheme 10). To the best of our knowledge, this reaction is the first example of the application of lipases in the resolution of unsaturated β-hydroxy esters; this method is a highly efficient one that provides operationally simple access to both enantiomers of these types of compounds.

To examine the tandem radical cyclization reactions, radical precursors (+)-**1d** were prepared from (R)-**6d** according to the method outlined in Scheme 2. After the radical cyclization of (+)-**1d**, the cis-6,5-fused ring product **3d** was isolated in high yield (75%) as a mixture of epimers (α:β = 1:1.6; Scheme 11). The relative configuration of α-**3d** was confirmed by the X-ray crystallographic analysis.[18] Oxidative elimination of the PhSe group from **3d** provided the exocyclic olefinic compound (−)-**4d**, which possesses three new chiral centers, in high optical purity (97.1% ee).

Scheme 12 provides an explanation of the stereochemical outcome of the cyclization of **1d**. The less-substituted side of the olefin group approaches the radical center via transition state **D1** to give a 6-endo cyclization intermediate, which undergoes a 5-exo cyclization via transition states **D2** and **D3** to produce the two epimers of the group transfer cyclization products **α-3d** and ***β*-3d**, respectively.

SCHEME 12



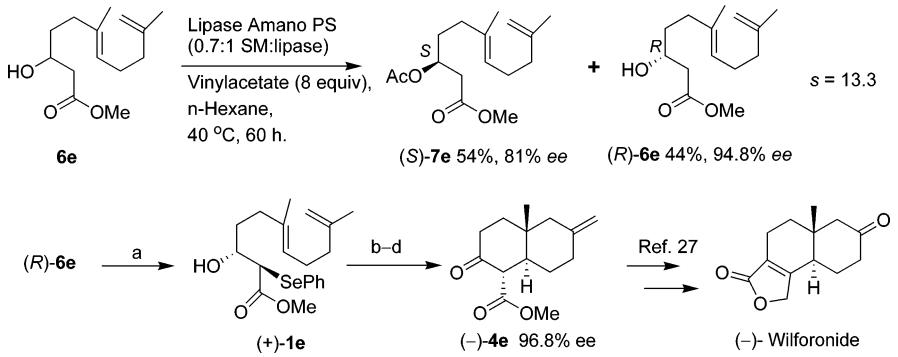
Formal Total Synthesis of (−)-Wilforonide. Wilforonide, a terpenoid isolated from the Chinese medicinal herb *Triperygium wilfordii* Hook F (Lei Gong Teng), has significant antiinflammatory activity and is effective in inhibiting T-cell proliferation and cytokine release.[26] To demonstrate the synthetic advantages of our Et_2AlCl-promoted phenylseleno group transfer radical cyclization reaction, we prepared compound (−)-**4e**, which we have used previously in our group as a key intermediate in the total synthesis of (−)-wilforonide.[27] By using the transesterification method described above, we readily obtained the chiral β-hydroxy esters (R)-**6e** in 44% yield and 94.8% ee (Scheme 13). The chiral radical precursor

(25) Bornscheuer, U.; Herar, A.; Kreye, L.; Wendel, V.; Capewell, A.; Meyer, H. H.; Scheper, T.; Kolisis, F. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1007−1016.

(26) (a) Chen, K.; Yang, R.; Wang, C. *Zhongcaoyao* **1986**, *17*, 242. (b) Lipsky, P. E.; Tao, X. L.; Cai, J.; Kovacs, W. J.; Olsen, N. J. U.S. Patent 5616458, 1997; *Chem. Abstr.* **1997**, *126*, 246818h. (c) Lipsky, P. E.; Tao, X. L.; Cai, J. U.S. Patent 5580562, 1996; *Chem. Abstr.* **1996**, *126*, 70141r. (d) Schkeryantz, J. M.; Luly, J. R.; Coghlan, M. J. *Synlett* **1998**, 723−724.

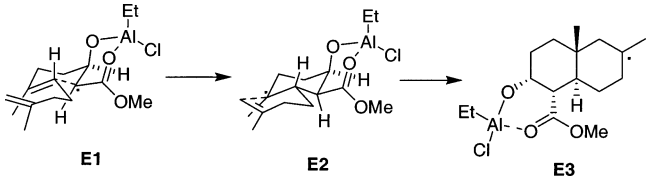
(27) Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785−1788.

SCHEME 13[a]



[a] Reagents and conditions: (a) LDA (2 equiv), THF, −35 °C, then PhSeBr, −78 °C, 80%; (b) Et_2AlCl (2 equiv), 30 °C, benzene, sunlamp, rt, 13 h; (c) H_2O_2, THF; (d) Dess−Martin reagent, CH_2Cl_2, 46% for three steps.

SCHEME 14



(+)-**1e** was prepared in 80% yield from (*R*)-**6e** by following the procedure outlined in Scheme 2. The cyclization of (+)-**1e** gave an inseparable mixture of products, but after two consecutive oxidations—i.e., the oxidative elimination of the PhSe group and the oxidation of the hydroxyl unit to give a ketone group—we isolated (−)-**4e** as the only bicyclic product. Compound (−)-**4e** is a core structure that is also found in many other naturally occurring bioactive terpenoids, such as andrographolide[28] and candelalides.[29] The successful extension of our asymmetric group transfer radical cyclization method to tandem reactions suggests that this process will be an attractive method for the asymmetric synthesis of multifunctional bicyclic compounds.

Scheme 14 provides an explanation for the stereochemical outcome of the cyclization of **1e**. The 6-endo-chairlike cyclization of the radical intermediate **E1** yields a six-membered cyclic radical **E2**, which undergoes another 6-endo-chairlike cyclization to form the bicyclic radical **E3** having a trans-6,6-ring junction.

(28) Puri, A.; Saxena, R.; Saxena, R. P.; Saxena, K. C.; Srivastava, V.; Tandon, J. S. *J. Nat. Prod.* **1993**, *56*, 995−999.

(29) Singh, S. B.; Zink, D. L.; Dombrowski, A. W.; Dezeny, G.; Bills, G. F.; Felix, J. P.; Slaughter, R. S.; Goetz, M. A. *Org. Lett.* **2001**, *3*, 247−250.

Conclusion

We have developed a new method of asymmetric phenylseleno group transfer radical cyclization of unsaturated β-hydroxy esters. Various unsaturated α-phenylseleno β-hydroxy esters underwent radical cyclization to give mono- and bicyclic group-transferred products in an efficient and highly regioselective and diastereoselective manner. To rationalize the high diastereoselectivities observed in this reaction, we propose a model based on chelation control of the aluminum alkoxides that are formed in situ. We devised a general method to prepare chiral radical precursors from which we obtained highly optically pure mono- and bicyclic group transfer products. The synthetic advantages of this method are demonstrated by our formal total synthesis of (−)-wilforonide. This paper presents the first examples of stereoselective group transfer radical cyclizations that occur via 1,2-asymmetric induction.

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Supporting Information Available: Experimental details; X-ray crystallographic data for compounds (−)-**3a** and α-**3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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