ORGANIC LETTERS

2007
Vol. 9, No. 3
469−472

Highly Stereoselective Construction of Spiro[4.5]decanes by SmI_2-Promoted Ketyl Radical Mediated Tandem Cyclization

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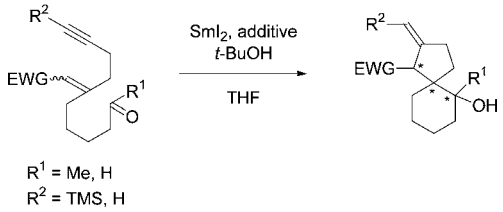
Received November 20, 2006

ABSTRACT

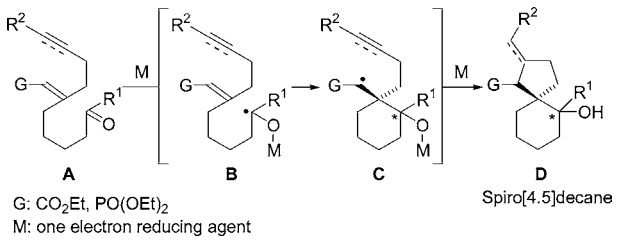


Ketyl radical mediated tandem cyclization of ω-alkynyl carbonyl compounds bearing activated alkene using SmI_2 gave spiro[4.5]decanes stereoselectively. In the presence of HMPA, α,β-unsaturated esters and alkenyl phosphonates were converted to spiro[4.5]decanes and a monocyclic compound, respectively. In the presence of Sm, bicyclic lactones were obtained from α,β-unsaturated esters. The spiro[4.5]-decane was provided from an alkenyl phosphonate. Interestingly, the stereochemical changeover at the first cyclization has been controlled by means of a variety of activators.

The spiro[4.5]decane scaffold is found in many naturally occurring products,[1] and hence various stereoselective methods for its synthesis have been developed.[2] Recently, we have reported a stereoselective approach to the highly functionalized spiro[4.5]decane skeleton by means of a Claisen rearrangement[3a,b] and its application to the synthesis of vetivane sesquiterpenes.[3c] As an alternative approach to the synthesis of spiro[4.5]decanes, we have been investigating a ketyl radical mediated tandem cyclization of a carbonyl compound, as shown in Scheme 1. Thus, the initial cyclization of ketyl radical intermediate **B**, derived by the reaction of the activated alkene-bearing ω-unsaturated carbonyl compound **A** with a one-electron reducing agent, followed by sequential radical cyclization of the resulting **C**, would provide spiro[4.5]decane **D**.

Enholm et al. reported an approach to a synthesis of spiro-[4.4]nonane based on a similar tandem cyclization triggered by *O*-stannyl ketyl radicals.[4] This reaction led to the desired

Scheme 1. Concept of Tandem Cyclization



(1) Reviews: Vandewalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1765−1831.

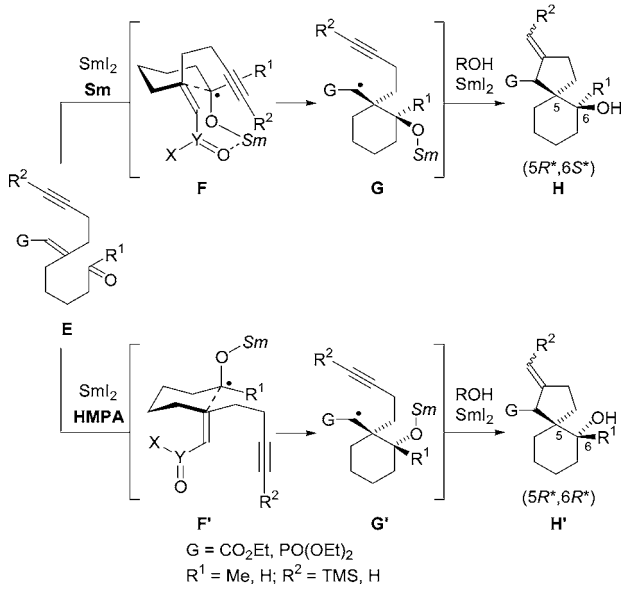
(2) For reviews on the synthesis of spirocyclic compounds, see: (a) Krapcho, A. P. *Synthesis* **1974**, 383−419. (b) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007−9071. (c) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779−828.

(3) (a) Nakazaki, A.; Miyamoto, H.; Henmi, K.; Kobayashi, S. *Synlett* **2005**, 1417−1420. (b) For a related example of the construction of spirocyclic compounds based on a Claisen rearrangement, see: Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274−2277. (c) Nakazaki, A.; Era, T.; Numada, Y.; Kobayashi, S. *Tetrahedron* **2006**, *62*, 6264−6271.

10.1021/ol0628255 CCC: $37.00
Published on Web 01/03/2007

spirocycles in moderate to high yields. However, poor stereoselectivities were observed. In contrast, the cyclization of alkene-bearing ketyl radicals, generated from alkenyl carbonyl compounds with SmI_2, enjoys widespread application in organic synthesis due to its ability to deliver both high yield and stereoselectivity.[5] In this context, SmI_2 is an obvious choice for our tandem cyclization strategy. It was also envisaged that stereochemical changeover at the first cyclization would be controlled by a variety of activators. In effect, the properties of activators, such as Sm metal[6] and HMPA,[7] would determine the stereochemical course of the cyclization owing to chelation control or dipolar repulsion in the ketyl radical intermediates **F** or **F′** (Scheme 2). In this

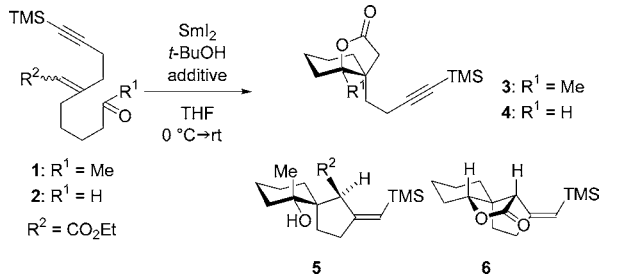
Scheme 2. Probable Stereochemical Outcomes for Tandem Cyclization



letter, we report our preliminary results for the tandem cyclizations of alkynyl carbonyl compounds, bearing various electron-withdrawing groups on the alkene, with SmI_2.

At the outset, we examined the ketyl radical mediated tandem cyclization of methyl ketone **1** and aldehyde **2** with SmI_2 in the presence of Sm metal or HMPA as an activator. The results thus obtained are summarized in Table 1. Attempted cyclization of ketone **1** with SmI_2 and Sm metal (3 equiv each) led us to the undesired bicyclic lactone **3** in good to excellent yield as a single isomer; none of the desired spiro[4.5]decanes were formed (entries 1 and 2). In contrast, the cyclization of aldehyde **2** was found to provide the related

Table 1. Tandem Cyclization of α,β-Unsaturated Esters with SmI_2



entry	substrate	additive	product	yield (%)[c,d]
1[a]	(*E*)-**1**	Sm	**3**	71
2[a]	(*Z*)-**1**	Sm	**3**	quant
3[a]	(*E*)-**2**	Sm	**4**	36
4[a]	(*Z*)-**2**	Sm	**4**	36
5[b]	(*E*)-**1**	HMPA	**5**	19
6[b]	(*Z*)-**1**	HMPA	**5**	29
7[b]	(*E*)-**2**	HMPA	**6**	43
8[b]	(*Z*)-**2**	HMPA	**6**	14

[a] Reactions were conducted in THF and *t*-BuOH (1 equiv) with SmI_2 (3 equiv) and Sm metal (3 equiv) at 0 °C for 1 h followed by warming to room temperature overnight. [b] Reactions were conducted in THF and *t*-BuOH (2 equiv) with SmI_2 (4 equiv) and HMPA (4 equiv) at 0 °C for 1 h followed by warming to room temperature overnight. [c] Isolated yield. [d] All products were of >95% dr, determined by ^1H NMR analysis.

lactone derivative **4** as a single isomer; however, the isolated yields were lower than for the ketone case (entries 3 and 4). Interestingly, the formation of the same lactones was independent of the alkenyl geometry in the cyclization precursors. We also attempted a similar tandem cyclization with 4 equiv of SmI_2 and 4 equiv of HMPA as an activator. Although the reaction of **1** and **2** provided the desired spiro-[4.5]decane **5** and **6**, respectively, as single isomers, it was in poor yield (entries 5−8). The stereochemistries of products 3−6 were determined through NOE experiments as shown in Figure 1, and it revealed that the relative stereochemistries

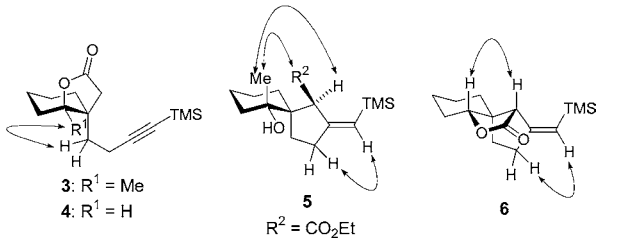


Figure 1. Stereochemical determinations of cyclized products by NOE experiments.

of the newly generated stereogenic centers in the first cyclization of lactones **3** and **4** are (5*R**,6*S**), which means the first cyclization proceeded through a chelation transition state, as anticipated. In contrast, the stereochemistries of spiro[4.5]decanes **5** and **6** are (5*R**,6*R**), which means that

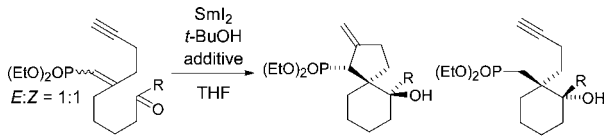
(4) Enholm, E. J.; Burroff, J. A. *Tetrahedron* **1997**, *53*, 13583−13602.
(5) For reviews of SmI_2-induced transformations, see: (a) Molander, A. G.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (b) Molander, A. G.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (c) Edmonds, D. J.; Johnson, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371−3403.
(6) (a) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729−8730. (b) Shinohara, I.; Okue, M.; Yamada, Y.; Nagaoka, H. *Tetrahedron Lett.* **2003**, *44*, 4649−4652.
(7) Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837−2840.

the ketyl radical mediated cyclization was governed by a nonchelation control.

On the basis of those results, it appears likely that due to stabilization of the α-carbonyl radical by means of the electron-withdrawing effect of the ester group the rate of the second radical cyclization with the alkyne is slower than that of its SmI_2-mediated one-electron reduction.[8]

We next examined the similar tandem cyclization of phosphonates **7** and **8**, which have a much lower electron-withdrawing nature than the ester. As expected, treatment of ketone **7** with SmI_2 and Sm metal was found to yield the desired spiro[4.5]decane **9** in 56% yield as a single isomer (Table 2, entry 1).[9,10] Furthermore, the similar tandem

Table 2. Tandem Cyclization of Alkenyl Phosphonates with SmI_2



7: R = Me
8: R = H

9: R = Me
10: R = H

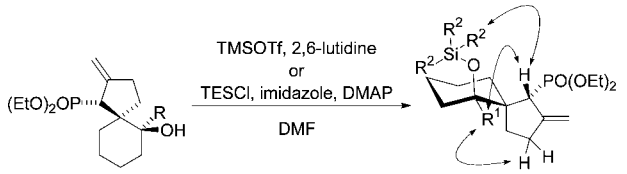
11: R = Me
12: R = H

entry	substrate	additive	product	yield (%)[c,d]
1[a]	**7**	Sm	**9**	56
2[a]	**8**	Sm	**10**	61
3[b]	**7**	HMPA	**11**	31
4[b]	**8**	HMPA	**12**	67

[a] Reactions were conducted in THF and *t*-BuOH (1 equiv) with SmI_2 (3 equiv) and Sm metal (3 equiv) at 0 °C for 1 h followed by warming to room temperature overnight. [b] Reactions were conducted in THF and *t*-BuOH (2 equiv) with SmI_2 (4 equiv) and HMPA (4 equiv) at −78 °C for 30 min. [c] Isolated yield. [d] All products were of >95% dr, determined by ^{1}H NMR analysis.

cyclization of aldehyde **8** proceeded to give us the corresponding spiro[4.5]decane **10** in moderate yield as a single isomer (entry 2). The relative stereochemistries of spiro[4.5]-decanes **9** and **10** were determined through NOE experiments on **13** and **14** derived from **9** and **10**, respectively, as depicted in Scheme 3. This revealed that the first cyclizations proceeded via a chelation transition state to give the (5*R**,6*S**)-isomer. In sharp contrast, when the reaction of **7** or **8** was conducted in the presence of HMPA, the monocyclic compounds **11** or **12** were obtained as single isomers, respectively. The relative stereochemistries of these compounds were determined through NOE experiments on bicyclic lactol **16** derived from **11** in two steps as shown in Scheme 4. Monocyclic compound **11** was converted to

Scheme 3. Stereochemical Determinations of Cyclized Products by NOE Experiments

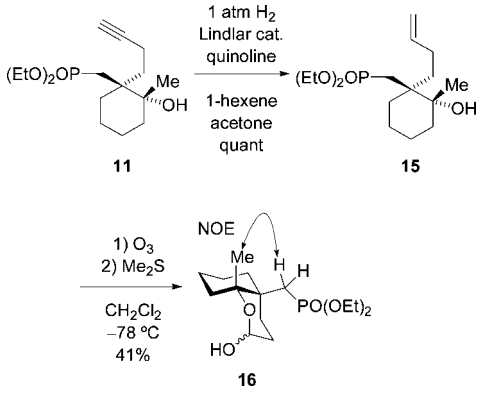


9: R = Me
10: R = H

13: R^1, R^2 = Me (82%)
14: R^1 = H, R^2 = Et (53%)

alkene **15** by hydrogenation.[11] Lactol **16** was obtained from **15** by ozonolysis. This revealed that, as in the case of the α,β-unsaturated esters, the relative stereochemistries of **9** and **11** are opposite to each other. We assume that the configuration of **12** is the same as that of **11**, as both are generated via similar transition states.

Scheme 4. Stereochemical Determinations of Cyclized Products by NOE Experiments



Mechanistic aspects of the above tandem cyclizations are shown in Scheme 5. The first cyclization is independent of the geometry of the alkene in the cyclization precursor, so the reaction sequence involves the common intermediates **G** or **G′**.

Thus, when using Sm metal as an activator for SmI_2, the samarium atom on the ketyl oxygen would chelate with the oxy functionality on the electron-withdrawing group in the ketyl intermediate **F** to afford the (5*R**,6*S**)-configuration of spirocyclic product **H**. In contrast, when using HMPA as an activator, its chelation would be prevented, thus rendering the (5*R**,6*R**)-spirocyclic product **H′** owing to an electronic effect. The mechanistic origins in terms of the C1 stereogenic center and the alkenyl geometry at the C2 position are still unclear.

In conclusion, we demonstrated ketyl radical mediated tandem cyclization of ketones and aldehydes containing α,β-unsaturated esters or phosphonate groups.

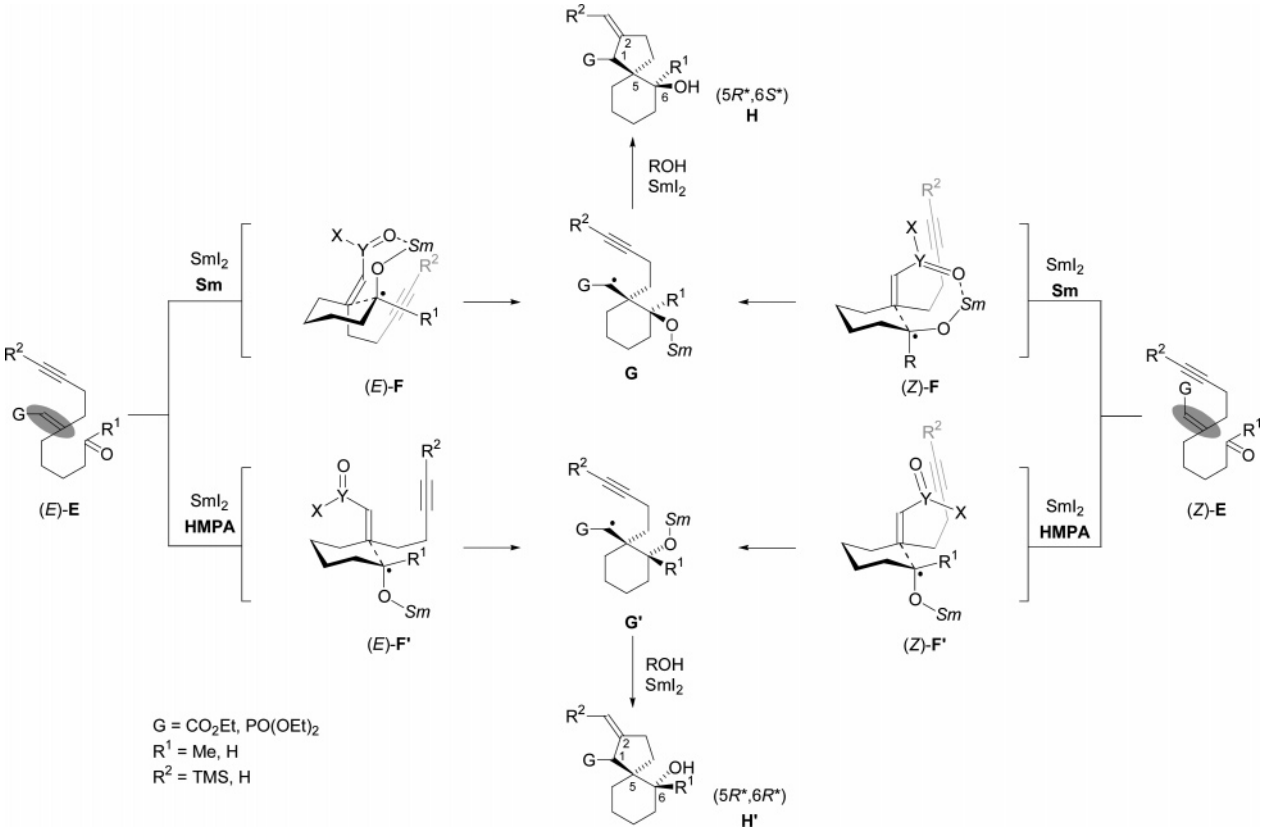
(8) (a) Curran, D. P. *Synthesis* **1988**, 417−439. (b) Curran, D. P. *Synthesis* **1988**, 489−513. (c) Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240−244. (d) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477−2480.

(9) Attempted tandem cyclization of the alkenylsilane derivatives [**1**, R^1 = Me, R^2 = $SiMe_3$, $SiMe_2$(2-furyl), $SiMe_2$(OMe), or $SiMe_2$Ph], the α,β-unsaturated amides [**1**, R^1 = Me, R^2 = $CONEt_2$, $CONMe_2$, CONMe(OMe), or CO(4-morpholine)], and the alkenyl sulfoxide derivative (**1**, R^1 = Me, R^2 = SOPh) did not afford the corresponding spiro[4.5]decanes.

(10) In the absence of Sm, the corresponding spiro[4.5]decane was obtained in lower yield.

(11) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046.

Scheme 5. Proposed Transition Structures of Tandem Cyclization



Of particular note, the phosphonates afforded the desired spiro[4.5]decanes in a highly stereoselective manner and moderate yield. This reaction is an effective method for the construction of functionalized spiro[4.5]decanes in a one-pot manner.

Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0628255