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Samarium(II)-Promoted Radical Spirocyclization onto an Aromatic Ring

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Samarium(II)-mediated spirocyclization onto an aromatic ring was achieved by the reaction of methyl 4-(4-oxoalkyl)benzoates with SmI_2 in the presence of *i*-PrOH and HMPA, yielding methyl 1-alkyl-1-hydroxyspiro[4.5]dec-6-ene-8-carboxylates in moderate to high yields. Utilizing this chemistry, spiro[3.5] and -[5.5] systems, and sterically congested spiro[4.5] systems, were easily synthesized. For the successful conversion, appropriate activation of the aromatic ring has proven to be extremely important: while an ester or amide functionality on the aromatic ring can promote the spirocyclization, a sulfonamide substituent causes *ortho* cyclization.

Introduction

Interest in spirocyclic systems derives from the unique molecular structure and diverse biological activities of this class of compounds. Among a number of synthetic methods of spirocycles,[1] those based on radical cyclization are often quite effective: spirocycles can be efficiently synthesized by an intramolecular radical attack onto a cyclic olefin,[2] intramolecular addition of tertiary cyclic radicals to an alkene[3] or alkyne,[4] or cyclization of a radical species possessing a preformed quaternary carbon center.[5] In contrast, synthesis of spirocycles by a radical attack onto an aromatic ring is relatively limited,[6,7] despite the availability of a wide range of aromatic compounds. This is presumably because of both the instability of spirocyclohexadienyl radical intermediate **A** (Scheme 1) and the reversible nature of the radical addition. The intermediate **A**, generated by the intramolecular addition of the X radical **1** onto an aromatic ring, can be easily converted into the Y radical **2** (aryl migration) or a more stable rearranged product **3**.[8] Numerous examples of intramolecular aryl migration from sulfur to carbon,[9] oxygen to carbon,[10] silicon to carbon,[11] and others[12] are reported, although control of the regioselectivity is sometimes difficult.[13] To realize the spirocyclization onto an aromatic ring, the spirohexadienyl radical intermediate **A** should be effectively trapped in an irreversible manner. Although some examples of formation of the spirocycle **4** with a loss of aromaticity by the capture of the intermediate **A** with an oxidant/nucleophile ($-e^-/Z^-$)[6] or a radical species ($Z^\bullet$)[7] have been

(1) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007−9071.

(2) (a) Middleton, D. S.; Simpkins, J. S. *Tetrahedron Lett*. **1988**, *29*, 1315−1318. (b) Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem*. **1993**, *58*, 3877−3885. (c) Zhang, W.; Pugh, G. *Tetrahedron Lett*. **1999**, *40*, 7595−7598. (d) Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett*. **2002**, *4*, 3329−3332.

(3) (a) Rao, A. V. R.; Rao, B. V.; Reddy, D. R.; Singh, A. K. *J. Chem. Soc., Chem. Commun*. **1989**, 400−401. (b) Rao, A. V. R.; Singh, A. K.; Reddy, K. M.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3171−3175. (c) Back, T. G.; Gladstone, P. L. *Synlett* **1993**, 699−700. (d) Kittaka, A.; Asakura, T.; Kuze, T.; Tanaka, H.; Yamada, N.; Nakamura, K. T.; Miyasaka, T. *J. Org. Chem*. **1999**, *64*, 7081−7093.

(4) (a) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem*. **1987**, *52*, 1339−1342. (b) Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun*. **1993**, 285−288. (c) Sha, C.-K.; Ho, W.-Y. *Chem. Commun*. **1998**, 2709−2710. (d) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069−2076.

(5) (a) Harling, J. D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun*. **1988**, 1380−1382. (b) Cossy, J.; Poitevin, C.; Pardo, D. G. *Synlett* **1998**, 251−252. (c) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem*. **1999**, *64*, 5504−5510. (d) Robertson, J.; Lam, H. W.; Abazi, S.; Roseblade, S.; Lush, R. K. *Tetrahedron* **2000**, *56*, 8959−8965.

(6) (a) Citterio, A.; Sebastiano, R.; Maronati, A.; Santi, R.; Bergamini, F. *J. Chem. Soc., Chem. Commun*. **1994**, 1517−1518. (b) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett*. **1997**, *38*, 5985−5988.

(7) (a) Hey, D. H.; Jones, G. H.; Perkins, M. J. *J. Chem. Soc. C* **1971**, 116−122. (b) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781−1784. (c) Yang, C.-C.; Chang, H.-T.; Fang, J.-M. *J. Org. Chem*. **1993**, *58*, 3100−3105. (d) Escolano, C.; Jones, K. *Tetrahedron Lett*. **2000**, *41*, 8951−8955. (e) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett*. **2000**, *2*, 2639−2641.

(8) (a) Glover, S. A.; Golding, S. L.; Goosen, A.; McCleland, C. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 842−848. (b) Narasimhan, N. S.; Aidhen, I. S. *Tetrahedron Lett*. **1988**, *29*, 2987−2988. (c) Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem*. **1998**, *63*, 537−542. (d) Crich, D.; Hwang, J.-T. *J. Org. Chem*. **1998**, *63*, 2765−2770. (e) Harrowven, D. C.; Nunn, M. I. T.; Newman, N. A.; Fenwick, D. R. *Tetrahedron Lett*. **2001**, *42*, 961−964.

(9) (a)Motherwell, W. B.; Pennell, A. M. K.; Ujjainwalla, F. *J. Chem. Soc., Chem. Commun*. **1992**, 1067−1068. (b) Harrowven, D. C. *Tetrahedron Lett*. **1993**, *34*, 5653−5656. (c) Bonfand, E.; Motherwell, W. B.; Pennell, A. M. K.; Uddin, M. K.; Ujjainwalla, F. *Heterocycles* **1997**, *46*, 523−534. (d) Studer, A.; Bossart, M. *Chem. Commun*. **1998**, 2127−2128. (e) Motherwell, W. B.; Vázquez, S. *Tetrahedron Lett*. **2000**, *41*, 9667−9671. (f) Bonfand, E.; Forslund, L.; Motherwell, W. B.; Vázquez, S. *Synlett* **2000**, 475−478.

(10) (a) Bachi, M. D.; Bosch, E. *J. Org. Chem*. **1989**, *54*, 1234−1236. (b) Lee, E.; Lee, C.; Tae, J. S.; Whang, H. S.; Li, K. S. *Tetrahedron Lett*. **1993**, *34*, 2343−2346. (c) Mander, L. N.; Sherburn, M. S. *Tetrahedron Lett*. **1996**, *37*, 4255−4258.

(11) (a) Studer, A.; Bossart, M.; Steen, H. *Tetrahedron Lett*. **1998**, *39*, 8829−8832. (b) Studer, A.; Bossart, M.; Vasella, T. *Org. Lett*. **2000**, *2*, 985−988. (c) Amrein, S.; Bossart, M.; Vasella, T.; Studer, A. *J. Org. Chem*. **2000**, *65*, 4281−4288.

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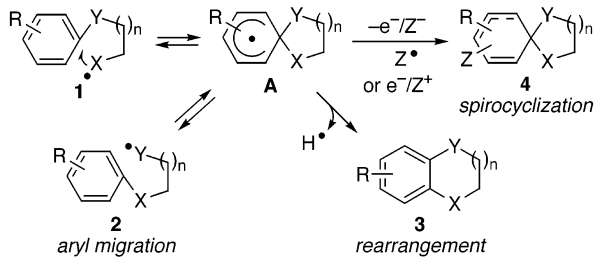
SCHEME 1

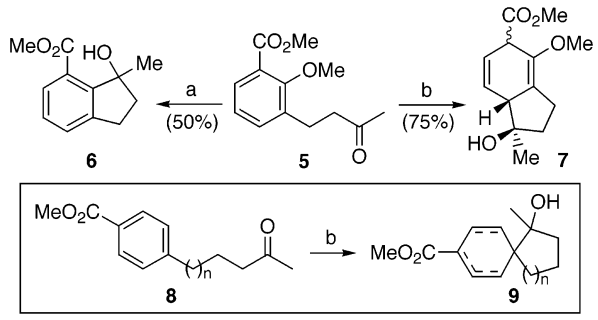


reported, reductive trapping of **A** (e^-/Z^+) is unknown. For such a reductive conversion, we expected that SmI_2/H^+ might be an ideal system.

Samarium(II)-mediated radical cyclization onto an arene ring had been unprecedented until recently. In 1995, Schmalz and co-workers reported the successful addition of ketyl radicals onto an arene−$Cr(CO)_3$ complex to form tricyclic products in good yields.[14] Reissig and co-workers reported samarium(II)-induced cyclization by ketyl radical addition onto an appropriately substituted arene ring to form 1,4-cyclohexadiene derivatives.[15] Furthermore, related radical *ortho* cyclization onto a formyl-substituted aryl ring was reported by Fang and co-workers.[16,17] However, samarium(II)-mediated spirocyclization onto an arene ring is unprecedented, although some spirocyclizations by the addition of the samarium ketyl radical onto a cyclic or conjugate olefin are reported.[18]

Recently, we found that a radical *ipso* substitution reaction of the aromatic methoxy group is effectively promoted by samarium(II) to afford cyclized products such as **6** (Scheme 2).[19] The detailed investigation

SCHEME 2[a]



[a] Reaction conditions: (a) SmI_2 (3.5 equiv), THF; (b) SmI_2 (5 equiv), HMPA (18 equiv), *i*-PrOH (2 equiv), THF, 0 °C.

revealed that addition of HMPA[20] to the reaction mixture dramatically changes the cyclization mode: thus, treatment of **5** with SmI_2 in the presence of HMPA and *i*-PrOH yielded a condensed ring, **7**, bearing a cyclohexadienyl moiety as a diastereomeric mixture.[21] On the basis of these results, we expected that the radical spirocyclization onto an aromatic ring could be possible starting from benzoate **8** possessing an oxoalkyl group at the position *para* to the ester group. Furthermore, the combination of SmI_2 and *i*-PrOH could also be an appropriate system for the above-mentioned reductive capture of the spirohexadienyl radical intermediate **A** (Scheme 1). In this paper, we present a full account of our investigation into the first radical spirocyclization onto an aromatic ring mediated by SmI_2.[22]

Results and Discussion

Synthesis of Requisite Substrates. Various benzoates bearing an alkyl ketone side chain were prepared starting from formylbenzoates **10**. Typically, as shown in Scheme 3, Wittig olefination of methyl 4-formylbenzoate (**10a**) followed by catalytic hydrogenation of the resulting alkene gave the acetal **11** in 61% yield, which was treated with PPTS in a mixed solvent of water and acetone to afford the corresponding aldehyde **12** in 99% yield. Reaction of **12** with an alkylmagnesium halide gave alcohols **13a**−**d**, followed by oxidation with Dess−Martin periodinane to afford the desired ketones **14a**−**d**. Similarly, as shown in Scheme 4, ketones **15**−**22** were synthesized starting from aldehydes **10a**−**e** (see the Supporting Information).

Heck olefination reaction of aryl halides **23** with appropriate alkenes is a convenient method for our substrate preparation (Scheme 5). Treatment of methyl 4-bromo-3-methylbenzoate (**23a**) with 4-penten-2-ol, *n*-Bu_4NCl, LiCl, and LiOAc in the presence of $Pd(OAc)_2$ in

(12) (a) Cadogan, J. I. G.; Hickson, C. L.; Hutchison, H. S.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1985**, 643−644. (b) Black, M.; Cadogan, J. I. G.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 395−396. (c) Lee, E.; Whang, H. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 913−914. (d) Amii, H.; Kondo, S.; Uneyama, K. *Chem. Commun.* **1998**, 1845−1846. (e) Wakabayashi, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 1899−1901. (f) Senboku, H.; Hasegawa, H.; Orito, K.; Tokuda, M. *Tetrahedron Lett.* **2000**, *41*, 5699−5703. (g) Clive, D. L. J.; Kang, S. *J. Org. Chem.* **2001**, *66*, 6083−6091.

(13) (a) Motherwell, W. B.; Pennell, A. M. K. *J. Chem. Soc., Chem. Commun.* **1991**, 877−879. (b) Leardini, R.; McNab, H.; Nanni, D. *Tetrahedron* **1995**, *51*, 12143−12158. (c) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137−140. (d) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 141−144. (e) Alcaide, B.; Rodríguez-Vicente, A. *Tetrahedron Lett.* **1998**, *39*, 6589−6592. (f) Wang, S.-F.; Chuang, C.-P.; Lee, J.-H.; Liu, S.-T. *Tetrahedron* **1999**, *55*, 2273−2288. (g) Ryokawa, A.; Togo, H. *Tetrahedron* **2001**, *57*, 5915−5921.

(14) (a) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2383−2385. (b) Schmalz, H.-G.; Kiehl, O.; Gotov, B. *Synlett* **2002**, 1253−1256. (c) Schwarz, O.; Brun, R.; Bats, J. W.; Schmalz, H.-G. *Tetrahedron Lett.* **2002**, *43*, 1009−1013.

(15) (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **1999**, *38*, 789−791. (b) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267−4277. (c) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290−1292. (d) Gross, S.; Reissig, H.-U. *Synlett* **2002**, 2027−2030.

(16) (a) Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643−4649. (b) Kuo, C.-W.; Fang, J.-M. *Synth. Commun.* **2001**, *31*, 877−892.

(17) For a related reaction, see: Yang, S. M.; Nandy, S. K.; Selvakumar, A. R.; Fang, J.-M. *Org. Lett.* **2000**, *2*, 3719−3721.

(18) (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624−625. (b) Shibuya, K.; Nagaoka, H.; Yamada, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1545−1546. (c) Merlic, C. A.; Walsh, J. C. *J. Org. Chem.* **2001**, *66*, 2265−2274. (d) Sono, M.; Nakashiba, Y.; Nakashima, K.; Takaoka, S.; Tori, M. *Heterocycles* **2001**, *54*, 101−104.

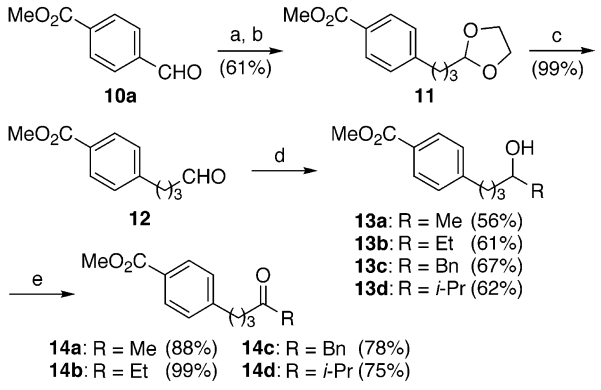
(19) Tanaka, T.; Wakayama, R.; Maeda, S.; Mikamiyama, H.; Maezaki, N.; Ohno, H. *Chem. Commun.* **2000**, 1287−1288.

(20) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485−1486. (b) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2000**, *122*, 7718−7722. (c) Knettle, B. W.; Flowers, R. A., II. *Org. Lett.* **2001**, *3*, 2321−2324. (d) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6895−6899.

(21) Ohno, H.; Wakayama, R.; Maeda, S.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909−5916.

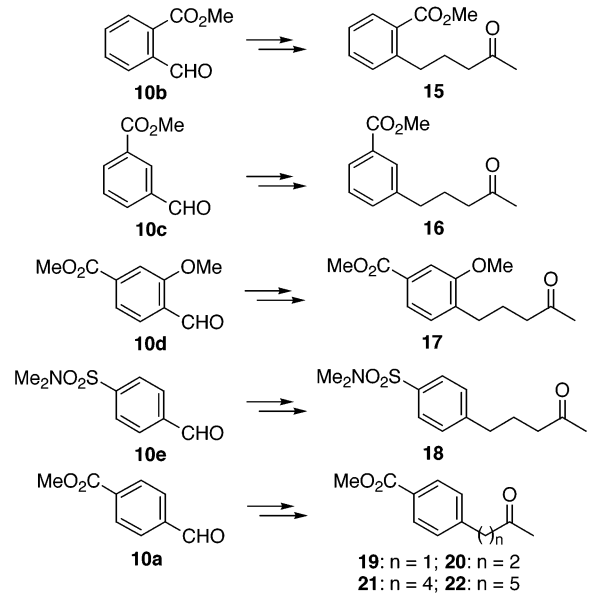
(22) For a preliminary communication, see: Ohno, H.; Maeda, S.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316−317.

SCHEME 3[a]



[a] Reagents: (a) $Ph_3P^+CH_2CH_2CH(-OCH_2CH_2O-)Br^-$, NaH, THF; (b) Pd/C, H_2, MeOH; (c) PPTS, H_2O, acetone; (d) RMgX, THF; (e) Dess−Martin periodinane, CH_2Cl_2.

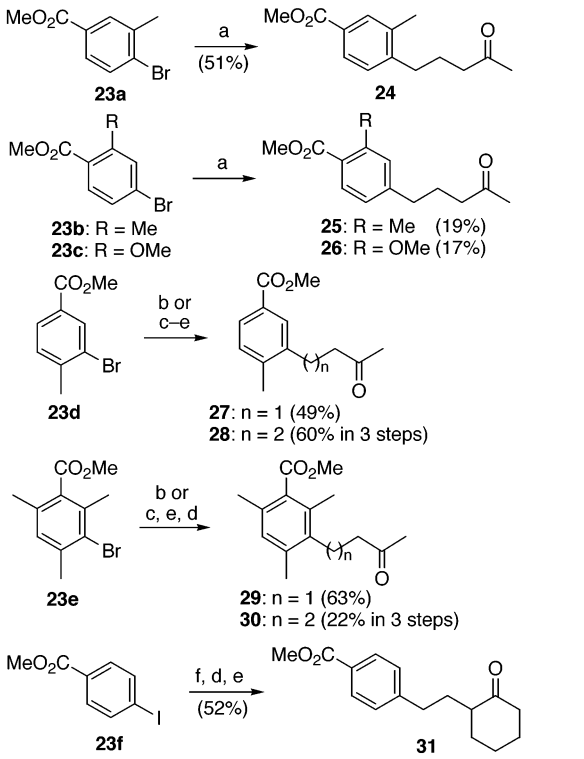
SCHEME 4



DMF[23] afforded methyl ketone **24** in a single step (51% yield). Similarly, ketones **25**, **26**, **27**, and **29** were synthesized directly from the corresponding aryl bromides **23b**, **23c**, **23d**, and **23e**, respectively, by the above palladium-catalyzed reaction with 4-penten-2-ol or 3-buten-2-ol. In contrast, since the reaction of methyl 3-bromo-4-methylbenzoate (**23d**) with 4-penten-2-ol under identical reaction conditions gave a complex mixture of unidentified products, we prepared **28** by a three-step sequence including the usual Heck olefination, catalytic hydrogenation, and Dess−Martin oxidation. Benzoate **31** possessing a cyclohexanone moiety was synthesized according to a similar three-step procedure including the Heck reaction of methyl 4-iodobenzoate (**23f**) with *trans*-2-vinylcyclohexanol.

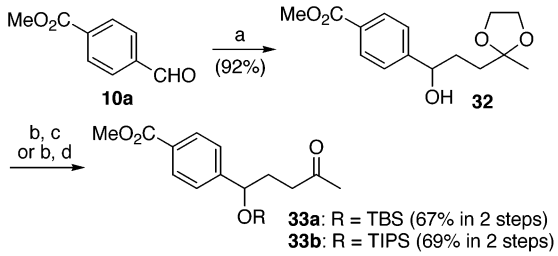
Methyl ketones **33a** and **33b** which bear a siloxy group on the benzylic position were easily synthesized by the reaction of **10a** with a Grignard reagent followed by cleavage of the ethylene acetal and silylation of the

SCHEME 5[a]



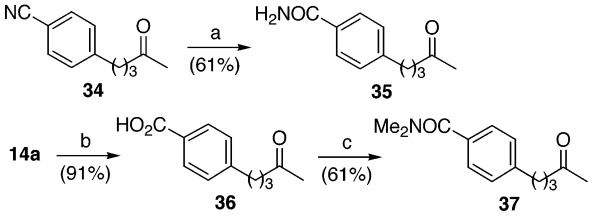
[a] Reagents: (a) 4-penten-2-ol, $Pd(OAc)_2$, n-Bu_4NCl, LiCl, $LiOAc\cdot 2H_2O$, DMF; (b) 3-buten-2-ol, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N; (c) 4-penten-2-ol, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N; (d) Pd/C, H_2, MeOH; (e) Dess−Martin periodinane, CH_2Cl_2; (4) *trans*-2-vinylcyclohexanol, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N.

SCHEME 6[a]



[a] Reagents: (a) $MeC(-OCH_2CH_2O-)CH_2CH_2MgBr$, THF; (b) PPTS, H_2O, acetone; (c) (TBS)Cl, imidazole, MeCN; (d) (TIPS)OTf, imidazole, DMF.

SCHEME 7[a]

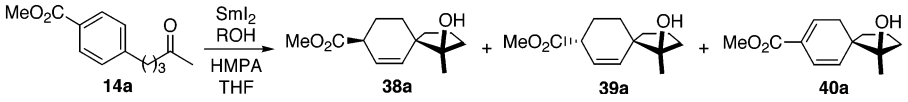


[a] Reagents: (a) 3% H_2O_2, 25% KOH; (b) $LiOH\cdot H_2O$, MeOH, H_2O; (c) $SOCl_2$, DMF, CH_2Cl_2, then 40% $NHMe_2$.

secondary hydroxy group with (TBS)Cl or (TIPS)OTf (Scheme 6). Finally, 4-substituted benzamide derivatives **35** and **37** were prepared by hydrolysis of the known nitrile **34**[15c] or hydrolysis of **14a** followed by amidation

(23) (a) Larock, R. C.; Leung, W.-Y.; Sandra, S.-D. *Tetrahedron Lett.* **1989**, *30*, 6629−6632. (b) Taylor, E. C.; Wang, Y. *Heterocycles* **1998**, *48*, 1537−1554.

TABLE 1. Optimization of the Reaction Conditions for the Spirocyclization of 14a[a]



entry	ROH	amt of HMPA (equiv)	temp	yield of **38a** + **39a** (%)	**38a**:**39a** ratio[c]	yield of **40a** (%)	recovery of **14a** (%)
1	*i*-PrOH	18	rt	84	2:1	0	0
2	*t*-BuOH	18	rt	68	2:1	0	0
3	H_2O	18	rt	9	2.5:1	0	33
4	BHT[b]	18	rt	12	2:1	17	19
5	none	18	rt	10	2:1	18	72
6	*i*-PrOH	0	rt	0		0	17
7	*i*-PrOH	10	rt	18	1:1.5	0	21
8	*i*-PrOH	18	0 °C	93	1:1.3	0	0
9	*i*-PrOH	18	−78 °C	84	1.7:1	0	0

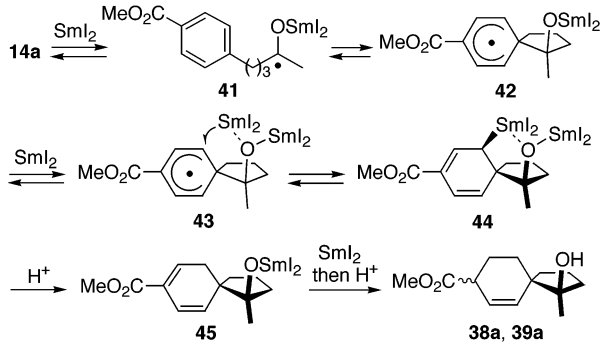
[a] All reactions were carried out in THF using 5 equiv of SmI_2 and 2 equiv of a proton source. [b] BHT = 2,6-di-*tert*-butyl-4-methylphenol. [c] Ratios were determined by ^1H NMR.

of the resulting acid **36** with thionyl chloride and an aqueous solution of dimethylamine, respectively (Scheme 7).

Spirocyclization of the *para*-Substituted Benzoate Derivatives. Having synthesized the requisite substrates, we next investigated the SmI_2-promoted cyclization of the benzoates **14a**. The results are summarized in Table 1. As we expected, treatment of **14a** with a THF solution of SmI_2 in the presence of HMPA (18 equiv) and *i*-PrOH (2 equiv) gave spirocyclic compounds **38a** and **39a** in 84% yield (**38a**:**39a** = 2:1, entry 1). Similarly, *t*-BuOH is an effective proton source for the spirocyclization (68% yield, entry 2). Although some other proton sources such as water or 2,6-di-*tert*-butyl-4-methylphenol (BHT)[24] were employed (entries 3 and 4), a considerable amount of the starting material was recovered or an intractable mixture of **38a**, **39a**, and dienylspirocycle **40a** was obtained. When the reaction was conducted in the absence of a proton source, only 10% of the spirocycles was obtained, and a considerable amount of the starting material (72%) was recovered (entry 5). Next, other conditions were investigated using 2 equiv of *i*-PrOH (entries 6−8). It was found that nearly 4 equiv of HMPA to SmI_2 is necessary for the complete conversion (compare entries 1, 6, and 7), which is in good agreement with the observations by Flowers and Hou that the addition of 4 equiv of HMPA to samarium iodide solution leads to a complex with strong reducing ability.[25] We found that lowering the reaction temperature to 0 °C increased the yield of **38a** and **39a** (93% yield, entry 8).

Relative configurations of the synthesized spirocycles were determined by NOE experiment and isomerization of the double bonds.[26] The configuration of the spirocyclic quaternary center and the neighboring quaternary carbon was completely controlled. One explanation for the observed stereochemical outcome is shown in Scheme 8.

SCHEME 8

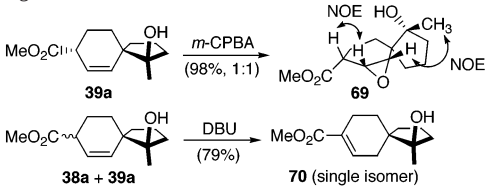


Cyclization of the ketyl radical intermediate **41** occurs onto the more reactive carbon (position *para* to the ester group) to give the unstable cyclohexadienyl radical intermediate **42**. Another molecule of SmI_2 reduces **42** by single-electron transfer from the side of the oxygen atom as depicted in **43**, and cyclohexadienyl anion **44**[27] will be produced stereoselectively. Finally, protonation of **44** followed by 1,4-reduction of the resulting enoate **45** by SmI_2[28] gives a diastereomixture of **38a** and **39a**. Considering the result that the spirocyclization reaction in the absence of *i*-PrOH afforded the recovered starting

(24) BHT is known as a selective protonating reagent for metal enolates; see: (a) Hou, Z.; Yoshimura, T.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11169−11170. (b) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1888−1889. (c) Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805−2508.

(25) (a) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137−1140. (b) Hou, Z.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1205−1206. See also: (c) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717−1720.

(26) An NOE experiment of epoxide **69** derived from **39a** showed reasonable correlations as shown below. Furthermore, treatment of a mixture of **38a** and **39a** with DBU afforded the corresponding isomerized product **70** as a single isomer in 79% yield. For the determination of relative configurations of other spirocycles, see the Supporting Information.



(27) For related intermediates, see: (a) Lin, S.-C.; Yang, F.-D.; Shiue, J.-S.; Yang, S.-M.; Fang, J.-M. *J. Org. Chem.* **1998**, *63*, 2909−2917. (b) Yang, S.-M.; Fang, J. M. *J. Org. Chem.* **1999**, *64*, 394−399.

(28) Inanaga and co-workers reported that sterically crowded α,β-unsaturated enoates undergo reduction of the double bond by SmI_2−HMPA; see: Inanaga, J.; Honda, Y.; Tabuchi, T.; Ohtsubo, K.; Yamaguchi, M.; Hanamoto, T. *Tetrahedron Lett.* **1991**, *32*, 6557−6558. For a related SmI_2-mediated 1,4-reduction of unsaturated acids, see: Concellón, J. M.; Rodríguez-Solla, H. *Chem.−Eur. J.* **2002**, *8*, 4493−4497.

TABLE 2. Samarium(II)-Mediated Spirocyclization of the *para*-Substituted Benzoates[a]

entry	substrate	product ratio (yield)[b] **38** (β-CO_2Me) : **39** (α-CO_2Me)
1	**14b**: R = Et	**38b**:**39b** = 1.4:1 (77%)
2	**14c**: R = Bn	**38c**:**39c** = 2:1 (74%)
3	**14d**: R = *i*-Pr	**38d**:**39d** = 1:2 (74%)
4	**12**: R = H	**38e**:**39e** = 1:1 (57%)
5	**20**	**38f**:**39f** = 1:2 (24%)
6	**21**	**38g**:**39g** = 1.6:1 (31%)
7	**31**	**38h**, **39h** (1.2:1, 58%)
8	**33a**: R = TBS	**38i**:**39i** = 1:2.2 (58%) other isomers (2.4:1, 28%)
9	**33b**: R = TIPS	**38j**, **39j** (1:2, 46%) other isomers (2:1, 27%)

[a] All reactions were carried out in THF at 0 °C under argon using SmI_2 (5 equiv) and *i*-PrOH. [b] Ratios were determined by ^{1}H NMR.

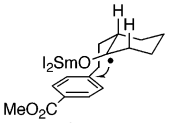
material with a small amount of the desired spirocyclized products (entry 5, Table 1), we anticipated that the reaction from **14a** to the cyclohexadienyl anion **44** would be a reversible process and that the protonation of **44** shifts the equilibrium to the product. This assumption is also supported by the reaction of **33a** (Table 2) in the presence of a larger amount of *i*-PrOH, which will be discussed below.

Next, spirocyclization of various *para*-substituted benzoates was investigated (Table 2). Similarly to the methyl ketone **14a** (entry 8, Table 1), ethyl and benzyl ketones **14b** and **14c** were cyclized into the corresponding spirocycles **38b** and **39b**, and **38c** and **39c**, respectively, by treatment with SmI_2 in the presence of HMPA and *i*-PrOH (entries 1 and 2). Sterically congested isopropyl ketone **14d** and less congested aldehyde **12b** also underwent spirocyclization under identical reaction conditions (entries 3 and 4). While the three- and seven-membered ring precursors **19** and **22** (Scheme 4) led to decomposition of the starting material, reaction of four- and six-membered ring precursors **20** and **21** afforded the desired spiro[3.5]nonenes **38f** and **39f** and spiro[5.5]undecenes **38g** and **39g**, respectively, although in low yields (24% and 31%, entries 5 and 6). This spirocyclization is extremely useful in that tricyclic spirocycles **38h** and **39h** can be obtained stereoselectively[29] in 58% yield by the reaction of cyclohexanone derivative **31**. Although the stereoselectivities were not satisfactory, sterically highly congested substrates **33a** and **33b** bearing a siloxy group on the benzylic position smoothly cyclized into the desired products **38i**, **39i**, and other isomers, and **38j**, **39j**, and other isomers, respectively (entries 8 and 9). It should be clearly noted that the cyclization of these congested siloxy derivatives **33a** and **33b** requires an increased amount of *i*-PrOH: for example, cyclization of **33a** in the presence of 2 equiv of *i*-PrOH yielded only 49% of the diastereomixture of the cyclized products along with the recovered starting material (19%), while the cyclization reaction using 24 equiv of *i*-PrOH smoothly proceeded to give an 86% yield of the desired products without recovering the starting material. These results also support the reversible nature of the spirocyclization reaction shown in Scheme 8.

Relative configurations of the cyclized products were determined by the base-mediated isomerization of the diastereomixtures and NOE analysis of the epoxide derivatives (see the Supporting Information). In all cases, the hydroxy group of the cyclized products directs the opposite side of the double bond of the cyclohexene moiety, which can be rationalized by the proposed mechanism shown in Scheme 8.

Effect of the Aromatic Substituents. From the above observations, *para*-substituted benzoates can be effectively cyclized into the desired spirocycles in a stereoselective manner by treatment with SmI_2 in the presence of HMPA and *i*-PrOH. Next, we investigated other benzoates including *ortho*- and *meta*-substituted ones. The results are summarized in Table 3. Reaction of the *ortho*-substituted benzoate **15** gave an inseparable mixture of the desired spiro compounds **46** (49% yield) and **47** (7% yield).[30] In this case, a small amount of a condensed ring, **48**, was obtained (8% yield) along with other unidentified products. Stereoselective formation of **46** and **47** can be rationalized as depicted in Scheme 9: formation of cyclohexadienyl anion **55**, protonation, and reduction of the double bond of the resulting **56** with SmI_2/HMPA[28] would produce a mixture of **46** and **47** both bearing a more stable α-CO_2Me group. The minor product **48** would be produced by the rearrangement of the cyclohexadienyl radical intermediate **A** (Scheme 1), followed by single-electron transfer by SmI_2. As we expected, cyclization of *meta*-substituted benzoate **16** af-

(29) Approach of the phenyl ring from the less hindered side (the opposite side of the axial protons) affords cyclized products with the observed stereochemistry.



(30) Although the separation of **46** and **47** was difficult at this stage, reduction of this mixture with $LiAlH_4$ afforded separable primary alcohols **71** and **72**. The relative configuration of **71** was determined by NOE analysis. Furthermore, hydrogenation of the mixture of **46** and **47** in the presence of catalytic Pd/C gave the corresponding spiro[4.5]decane derivative **73** as a single isomer.

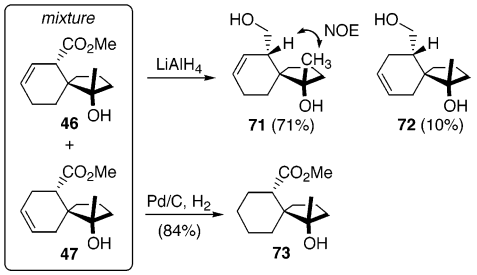
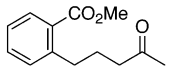
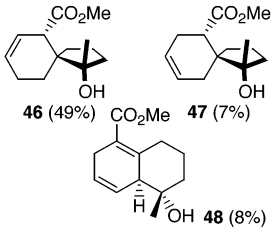
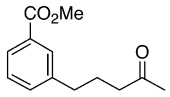
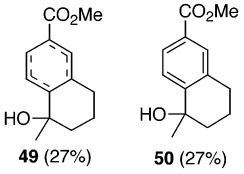
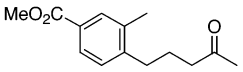
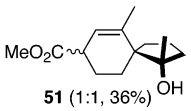
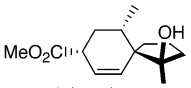
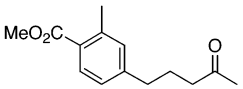
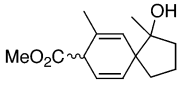
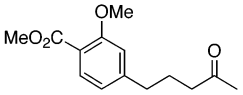
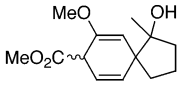
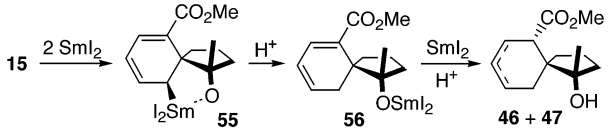


TABLE 3. Cyclization of Various Substituted Benzoates[a]

entry	substrate	products (yield)[b]
1	 **15**	 **46** (49%) **47** (7%) **48** (8%)
2	 **16**	 **49** (27%) **50** (27%)
3	 **24**	 **51** (1:1, 36%)  **52** (31%)
4	 **25**	 **53** (1:1, 79%)
5	 **26**	 **54** (3:1, 44%)

[a] All reactions were carried out in THF at 0 °C under argon using SmI_2 (5 equiv) and *i*-PrOH. [b] Ratios were determined by ^1H NMR.

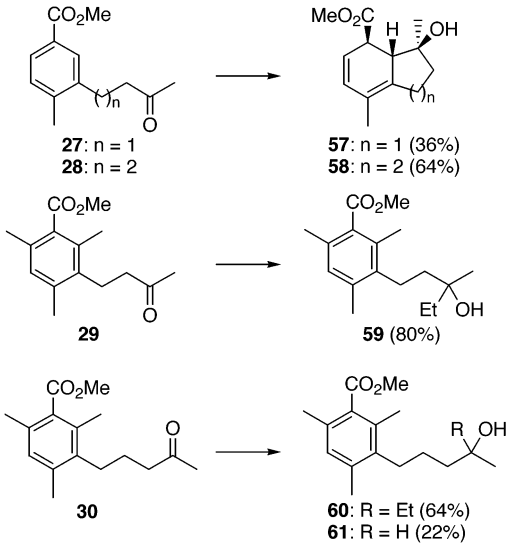
SCHEME 9



forded no spirocyclic compound (entry 2), yielding an unstable condensed cyclohexadiene, **49** (27% yield), and an aromatized compound, **50** (27% yield). The unstable diene **49** was gradually converted into the stable compound **50** during purification. When the one-pot oxidation was conducted with *p*-benzoquinone, the aromatized product **50** was obtained in 69% yield as the sole product. From these observations, the ketyl radicals can attack the substituted benzene ring at the position *para* or *ortho* to the ester group.

The cyclization of benzoates such as **16** to condensed rings has proven to be extremely sensitive to the substituents on the aromatic ring. As shown in Scheme 10, 4-methylbenzoate derivatives **27** and **28** cyclized onto the carbon *ortho* to the ester group instead of the methylated *para* carbon to afford the cyclized products **57** and **58**, respectively. However, when 2,4,6-trimethylbenzoate

SCHEME 10

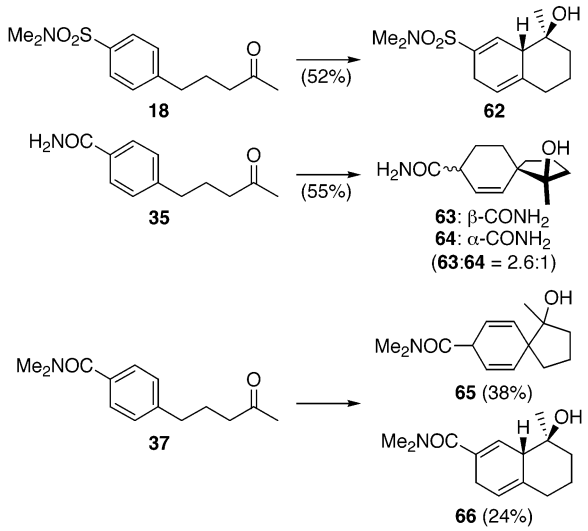


derivatives **29** and **30** were used, the ethylated products **59** and **60** were mainly obtained (80% and 64% yield, respectively). Although such ethylation is unprecedented as far as we are aware, it would be possible by the action of diiodoethane, which is used for preparation of the SmI_2 solution. It is extremely interesting that the cyclization of *meta*-substituted benzoates such as **16** (Table 3) and **27** and **28** (Scheme 10) to the condensed rings proceeds only when the reacting aromatic carbon is unsubstituted, while the *para*-substituted benzoates cyclized into spirocycles by the radical attack onto the substituted aromatic carbon (Tables 1 and 2).

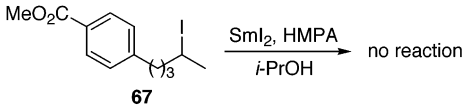
Reaction of benzoates **24** and **25** (entries 3 and 4, Table 3) bearing a methyl group on the aromatic ring with SmI_2 in the presence of HMPA and *i*-PrOH yielded spirocycles **51** and **52**, and **53**, respectively, in good yields. In contrast, 3-methoxybenzoate derivative **17** (Scheme 4) produced no spirocycle under identical reaction conditions, while *o*-methoxybenzoate **26** yielded **54** as a 3:1 diastereomixture in a moderate yield (entry 5). This trend is in good accordance with Reissig's results: a related samarium-mediated cyclization onto a methoxy-substituted aromatic ring regioselectively occurs at the position *meta* to the methoxy group.[31] For a reason that is unclear, *ortho*-substituted benzoates **25** and **26** yield the cyclohexadiene derivatives **53** and **54**.

Next, activation of the arene ring by electron-withdrawing groups other than the ester group was investigated (Scheme 11). Exposure of the sulfonamide **18** to the typical samarium-mediated cyclization conditions gave a condensed ring, **62**, in a stereoselective manner. In contrast, the carboxamide **35** was easily cyclized into the desired spirocycles **63** and **64** (2.6:1) in 55% yield. Reaction of *N*,*N*-dimethylcarboxamide **37** afforded a spirocycle, **65**, with a cyclohexadiene moiety in 38% yield, along with a condensed ring, **66** (24% yield). As one can expect, the substrate without the ester group (5-phenylpentan-2-one) gave no cyclized product. Considering these results and Reissig's observations using cyano-substituted substrates,[31] an appropriate tuning of the electronic density of the aromatic ring is extremely important for

SCHEME 11



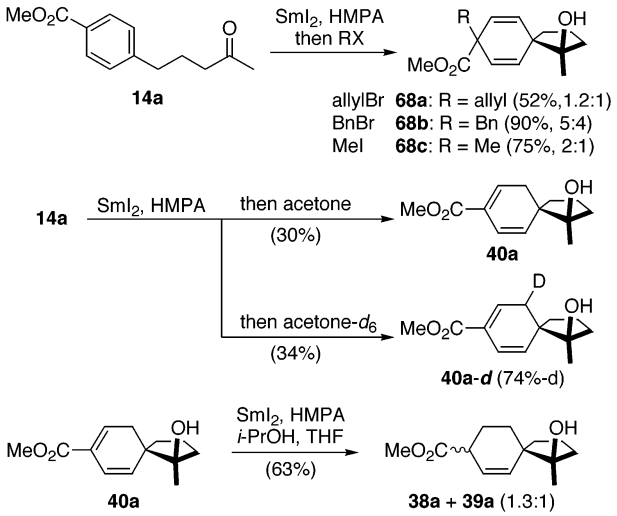
SCHEME 12



the present samarium-promoted spirocyclization onto an aromatic ring. Furthermore, the samarium ketyl radical has proven to also be important for the spirocyclization: exposure of the corresponding iodide **67** to the cyclization conditions led to recovery of the starting material (Scheme 12). This result clearly demonstrates that the success of the spirocyclization would be attributed to (1) the relative persistence of ketyl radicals compared to alkyl radicals under the reducing conditions, which provides more time for the cyclization to occur, and (2) the perceived reversibility of single-electron transfer to the carbonyls from samarium(II), which minimizes side reactions by suppressing the concentration of the ketyl radical.[32]

Finally, to expand the synthetic utility of the spirocyclization and to understand the reaction mechanism, we investigated capture of the cyclohexadienyl anion intermediate by electrophiles (Scheme 13). When the ketone **14a** was treated with SmI_2 and HMPA in the absence of any proton source followed by addition of allyl bromide, benzyl bromide, or iodomethane, the expected cyclohexadienes **68a**−**c** were obtained in moderate to good yields

SCHEME 13



(52−90% yield). Interestingly, when acetone was added instead of the alkyl halide, the conjugated diene **40a** was obtained. When acetone-d_6 was employed, incorporation of deuterium was observed to give **40a**−***d*** (74% D). This is presumably due to the reversible nature of this aldol-type reaction of a highly stabilized cyclopentadienyl anion with acetone. Furthermore, acetone would quench the SmI_2 to suppress the 1,4-reduction of the conjugated diene **40a** (Scheme 8).

We proposed that a diene such as **40a** would be an important intermediate for the present spirocyclization (Scheme 8). Since the diene **40a** was isolated in a pure form, we subjected **40a** to the samarium-mediated cyclization conditions. As we expected, treatment of the diene **40a** afforded the reduced products **38a** and **39a** (1.3:1) in 63% yield, which is in good agreement with the mechanism shown in Scheme 8.

Conclusion

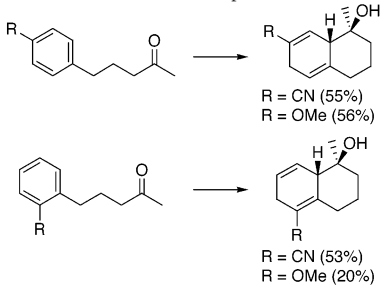
In conclusion, we have developed samarium(II)-mediated spirocyclization onto an aromatic ring. This reaction can serve as a stereoselective synthetic route to spirocyclic compounds including spiro[3.5]nonenes, spiro[4.5]-decenes, and spiro[5.5]undecenes starting from readily available aromatic compounds. Introduction of an appropriate electron-withdrawing group such as an ester or amide group on the aromatic ring is necessary for the successful spirocyclization. It is strongly suggested that the spirocyclization would proceed through both the formation of a cyclohexadienyl anion intermediate and 1,4-reduction of the cyclohexadiene intermediate.

Experimental Section

Compounds **23e**,[33] 2-(2-bromoethyl)-2-methyl-1,3-dioxolane,[34] and **34**[15c] were synthesized according to the literature.

General Procedure for the Wittig Reaction Followed by Palladium-Catalyzed Hydrogenation. Synthesis of Methyl {4-[3-(2,5-Dioxolanyl)]propyl}benzoate (11). To a solution of 2-[1,3-dioxolan-2-yl)ethyl]triphenyphosphonium bromide [$Ph_3P^+CH_2CH_2CH(-OCH_2CH_2O-)Br^-$; 19.6 g, 44.1 mmol] in THF (100 mL) was added NaH (1.76 g, 44.1 mmol) at 0 °C.

(31) Recently, Reissig and co-workers reported the related ketyl radical cyclization onto the aromatic ring activated by a methoxy or cyano group.[15c] In all cases, the position *meta* to the methoxy or cyano group is more reactive than the other positions.



(32) (a) Curran, D. P. *Chemtracts: Org. Chem.* **1994**, *7*, 351−354. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186−3192.

(33) Hart, H.; Janssen, J. F. *J. Org. Chem.* **1970**, *35*, 3637−3641.

(34) Petroski, R. J. *Synth. Commun.* **2002**, *32*, 449−455.

After the mixture was stirred for 30 min at this temperature, a solution of the aldehyde **10a** (7.24 g, 44.1 mmol) in THF (20 mL) was added to the mixture, and stirring was continued for 1 h. Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (5:1) to give the corresponding alkene (9.86 g, 90% yield). This alkene (9.86 g, 39.7 mmol) was then subjected to catalytic hydrogenation in MeOH (90 mL) using Pd/C (423 mg) under atmospheric pressure of hydrogen at room temperature for 30 min. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to an oil, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (5:1) to give the acetal **11** (6.76 g, 61% yield in two steps) as a colorless oil: IR (KBr, cm^{-1}) 1720 (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.63−1.80 (m, 4H, 2′-CH_2 and 3′-CH_2), 2.68 (t, J = 7.5 Hz, 2H, 1′-CH_2), 3.76−3.93 (m, 4H, OCH_2CH_2O), 3.86 (s, 3H, OMe), 4.83 (t, J = 4.5 Hz, 1H, 1″-H), 7.23 (d, J = 8.1 Hz, 2H, Ar), 7.93 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 32.9, 35.3, 51.5, 64.4 (2C), 103.8, 127.4, 128.0 (2C), 129.3 (2C), 147.3, 166.5; MS (EI) *m*/*z* (rel intens) 250 (M^+, 3), 73 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1236.

General Procedure for the Cleavage of Ethylene Acetals. Synthesis of Methyl 4-(4-Oxobutyl)benzoate (12). To a stirred solution of the acetal **11** (980 mg, 3.92 mmol) in a mixed solvent of acetone (18 mL) and water (12 mL) was added PPTS (98.4 mg, 0.392 mmol), and the mixture was stirred under reflux for 12 h. Saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give the aldehyde **12**[35] (797 mg, 99% yield) as a colorless oil: IR (KBr, cm^{-1}) 1720 (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (tt, J = 7.5, 7.2 Hz, 2H, 2′-CH_2), 2.46 (t, J = 7.2 Hz, 2H, 3′-CH_2), 2.70 (t, J = 7.5 Hz, 2H, 1′-CH_2), 3.90 (s, 3H, OMe), 7.24 (d, J = 7.5 Hz, 2H, Ar), 7.96 (d, J = 7.5 Hz, 2H, Ar), 9.76 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 34.8, 42.9, 51.9, 128.0, 128.4 (2C), 129.7 (2C), 146.7, 166.9, 201.8; MS (EI) *m*/*z* (rel intens) 206 (M^+, 13), 162 (100); HRMS (EI) *m*/*z* calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0942.

General Procedure for the Grignard Reaction. Synthesis of Methyl 4-(4-Hydroxypentyl)benzoate (13a). To a stirred solution of the aldehyde **12** (2.57 g, 12.5 mmol) in THF (30 mL) was added MeMgBr (0.93 M in THF; 13.4 mL, 12.5 mmol) at −40 °C, and the mixture was stirred for 1 h. Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give the alcohol **13a** (1.55 g, 56% yield) as a colorless oil: IR (KBr, cm^{-1}) 3371 (OH), 1720 (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 6.0 Hz, 3H, CMe), 1.44−1.86 (m, 5H, 2′-CH_2, 3′-CH_2 and OH), 2.69 (t, J = 7.5 Hz, 2H, 1′-CH_2), 3.77−3.88 (m, 1H, 4-H), 3.90 (s, 3H, OMe), 7.25 (d, J = 8.1 Hz, 2H, Ar), 7.95 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 27.1, 35.7, 38.6, 51.9, 67.6, 127.6, 128.3 (2C), 129.5 (2C), 147.9, 167.1; MS (EI) *m*/*z* (rel intens) 222 (M^+, 8), 162 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1261.

General Procedure for Dess−Martin Oxidation. Synthesis of Methyl 4-(4-Oxopentyl)benzoate (14a). To a stirred solution of the alcohol **13a** (1.55 g, 6.98 mol) in CH_2Cl_2 (30 mL) was added Dess−Martin periodinane (2.96 g, 6.98 mol) at room temperature, and the mixture was stirred for 30 min. Saturated $NaHCO_3$ and $Na_2S_2O_3$ were added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give the known ketone **14a**[36] (1.35 g, 88% yield) as a colorless oil.

General Procedure for the Palladium-Catalyzed Direct Synthesis of Ketones from Aryl Bromides 23. Synthesis of Methyl 3-Methyl-4-(4-oxopentyl)benzoate (24). To a stirred solution of the aryl bromide **23a** (729 mg, 3.18 mmol) in DMF (6.4 mL) were successively added 4-penten-2-ol (0.491 mL, 4.77 mmol), $Pd(OAc)_2$ (322 mg, 1.43 mmol), *n*-Bu_4NCl (1.77 g, 6.36 mmol), LiCl (135 mg, 3.18 mmol), and $LiOAc·2H_2O$ (812 mg, 7.95 mmol), and the mixture was stirred at 100 °C for 55 h. After cooling, saturated NH_4Cl was added to the mixture, and the whole was extracted with Et_2O. The extract was dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (5:1). Further purification by column chromatography over silica gel with $CHCl_3$–acetone (2:1) gave the ketone **24** (379 mg, 51% yield) as a colorless oil: IR (KBr, cm^{-1}) 1716 (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (tt, J = 7.5, 7.5 Hz, 2H, 2′-CH_2), 2.14 (s, 3H, CMe), 2.35 (s, 3H, CMe), 2.49 (t, J = 7.5 Hz, 2H, 3′-CH_2), 2.65 (t, J = 7.5 Hz, 2H, 1′-CH_2), 3.89 (s, 3H, OMe), 7.18 (d, J = 7.8 Hz, 1H, Ar), 7.79 (d, J = 7.8 Hz, 1H, Ar), 7.82 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.6, 30.0, 32.5, 42.9, 51.9, 127.2, 127.9, 128.9, 131.3, 136.2, 145.4, 167.2, 208.3; MS (EI) *m*/*z* (rel intens) 234 (M^+, 19), 106 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1251.

General Procedure for the Synthesis of Ketones Using the Usual Heck Reaction. Synthesis of Methyl 4-Methyl-3-(4-oxopentyl)benzoate (28) via Methyl 3-(4-Hydroxypentyl)-4-methylbenzoate. To a stirred solution of the aryl bromide **23d** (160 mg, 0.70 mmol) in Et_3N (0.2 mL) were successively added 4-penten-2-ol (0.18 mL, 1.75 mmol), $Pd(OAc)_2$ (16 mg, 0.07 mmol), and P(*o*-tol)$_3$ (43 mg, 0.14 mmol), and the mixture was stirred at 75 °C for 21 h. After cooling, water was added to the mixture, and the whole was concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give the corresponding styrene derivative. This styrene derivative was then subjected to catalytic hydrogenation in MeOH (2 mL) using Pd/C (8 mg) under atmospheric pressure of hydrogen at room temperature for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to an oil, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give methyl 3-(4-hydroxypentyl)-4-methylbenzoate (114 mg, 70% yield in two steps): colorless oil; IR (KBr, cm^{-1}) 3028 (OH), 1720 (C═O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J = 6.3 Hz, 3H, CMe), 1.48−1.77 (m, 5H, 2′-CH_2, 3′-CH_2, and OH), 2.35 (s, 3H, CMe), 2.61−2.70 (m, 2H, 1′-CH_2), 3.84 (tq, J = 6.3, 6.3 Hz, 1H, 4′-H), 3.89 (s, 3H, OMe), 7.19 (d, J = 8.0 Hz, 1H, Ar), 7.76 (d, J = 8.0 Hz, 1H, Ar), 7.81 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 23.6, 26.2, 33.0, 39.0, 51.9, 67.9, 127.1, 127.8, 129.8, 130.2, 140.7, 141.6, 167.4; MS (EI) *m*/*z* (rel intens) 236 (M^+, 9), 176 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1393.

By a procedure identical with that described for the synthesis of **14a** from **13a**, methyl 3-(4-hydroxypentyl)-4-methylbenzoate (114 mg, 0.48 mmol) was converted into the ketone **28** (97 mg, 86% yield): colorless oil; IR (KBr, cm^{-1}) 1718

(35) DeGraw, J. 1.; Tagawa, H.; Christie, P. H.; Lawson, J. A.; Brown, E. G. *J. Heterocycl. Chem.* **1986**, *23*, 1−4.

(36) Kise, N.; Suzumoto, T.; Shono, T. *J. Org. Chem.* **1994**, *59*, 1407−1413.

(C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (tt, J = 8.0, 8.0 Hz, 2H, 2′-CH_2), 2.14 (s, 3H, CMe), 2.36 (s, 3H, CMe), 2.50 (t, J = 8.0 Hz, 2H, CH_2), 2.64 (t, J = 8.0 Hz, 2H, CH_2), 3.90 (s, 3H, OMe), 7.20 (d, J = 8.0 Hz, 1H, Ar), 7.77 (d, J = 8.0 Hz, 1H, Ar), 7.79 (s, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 23.7, 29.9, 32.3, 42.9, 51.8, 127.3, 127.8, 129.9, 130.3, 140.0, 141.7, 167.2, 208.8; MS (EI) m/z (rel intens) 234 (M^+, 41), 177 (100); HRMS (EI) m/z calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1273.

Methyl 4-[1-Hydroxy-3-(2-methyl-1,3-dioxolan-2-yl)-propyl]benzoate (32). To a vigorously stirring mixture of magnesium (125 mg, 5.12 mmol) and THF (3 mL) was added a solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[34] (1.0 g, 5.13 mmol) in THF (3 mL), and the mixture was slightly heated. After the exothermic reaction was completed, the mixture was stirred for 10 min at room temperature. The aldehyde **10a** (421 mg, 2.56 mmol) was added to the mixture at 0 °C, and the mixture was stirred for 2 h at 0 °C and a further 1 h at room temperature. Saturated NH_4Cl was added to the mixture, and the whole was extracted with Et_2O. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with n-hexane−EtOAc (3:1) to give the alcohol **32** (662 mg, 92% yield) as a colorless oil: IR (KBr, cm^{-1}) 3462 (OH), 1722 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 3H, CMe), 1.66−1.86 (m, 4H, 2′-CH_2 and 3′-CH_2), 3.31 (br s, 1H, OH), 3.90 (s, 3H, OMe), 3.92−3.95 (m, 4H, OCH_2CH_2O), 4.73 (dd, J = 5.5, 5.0 Hz, 1H, 1′-H), 7.40 (d, J = 8.0 Hz, 2H, Ar), 7.98 (d, J = 8.0 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 33.2, 34.9, 51.9, 64.47, 64.50, 73.5, 109.7, 125.6 (2C), 128.9, 129.6 (2C), 150.0, 167.0; MS (FAB) m/z (rel intens) 303 (MNa^+, 74), 219 (100); HRMS (FAB) m/z calcd for $C_{15}H_{20}NaO_5$ (MNa^+) 303.1209, found 303.1203.

Methyl 4-[1-(*tert*-Butyldimethylsilyloxy)-4-oxopentyl]-benzoate (33a). To a stirred solution of the acetal **32** (726 mg, 2.59 mmol) in a mixed solvent of acetone (12 mL) and water (8 mL) was added PPTS (65 mg, 0.26 mmol), and the mixture was stirred under reflux overnight. Saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with n-hexane−EtOAc (2:1) to give the corresponding ketone (486 mg, 79% yield). This ketone (250 mg, 1.06 mmol) was treated with (TBS)Cl (191 mg, 1.27 mmol) and imidazole (180 mg, 2.65 mmol) in MeCN (0.5 mL) at 40 °C for 2 h. Water was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with n-hexane−EtOAc (10:1) to give the silyl ether **33a** (317 mg, 67% yield in two steps) as a colorless oil: IR (KBr, cm^{-1}) 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.17 (s, 3H, SiMe), 0.00 (s, 3H, SiMe), 0.87 (s, 9H, CMe_3), 1.82−1.99 (m, 2H, 2′-CH_2), 2.09 (s, 3H, CMe), 2.36 (ddd, J = 17.8, 8.5, 5.5 Hz, 1H, 3′-C*H*H), 2.51 (ddd, J = 17.8, 8.3, 6.8 Hz, 1H, 3′-CH*H*), 3.89 (s, 3H, OMe), 4.78 (dd, J = 6.5, 5.0 Hz, 1H, 1′-H), 7.35 (d, J = 8.3 Hz, 2H, Ar), 7.97 (d, J = 8.3 Hz, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.14, −4.83, 18.1, 25.7 (3C), 29.9, 34.0, 38.8, 51.9, 73.1, 125.7 (2C), 128.9, 129.5 (2C), 150.1, 166.9, 208.3. Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.23; H, 8.58.

4-(4-Oxopentyl)benzamide (35). A mixture of the nitrile **34**[15c] (1.26 g, 6.65 mmol), 3% H_2O_2 (34.2 g), and 25% KOH (1.9 g) was heated at 45 °C and stirred at room temperature for 3 h. The crystalline mass was collected by filtration and purified by column chromatography over silica gel with EtOAc to give the amide **35** (835 mg, 61% yield) as colorless crystals: mp 119 °C; IR (KBr, cm^{-1}) 3390 ($CONH_2$), 3197 ($CONH_2$), 1709 (C=O), 1645 ($CONH_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (tt, J = 7.8, 7.3 Hz, 2H, 2′-CH_2), 2.12 (s, 3H, CMe), 2.44 (t, J = 7.3 Hz, 2H, CH_2), 2.67 (t, J = 7.8 Hz, 2H, CH_2), 6.23 (br s, 2H, NH_2), 7.24 (d, J = 8.0 Hz, 2H, Ar), 7.75 (d, J = 8.0 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 29.9, 34.8, 42.6, 127.5 (2C), 128.6 (2C), 131.1, 146.0, 169.5, 208.5; MS (EI) m/z (rel intens) 205 (M^+, 31), 131 (100); HRMS (EI) m/z calcd for $C_{12}H_{15}NO_2$ 205.1103; found 205.1104.

4-(4-Oxopentyl)benzoic Acid (36). To a stirred solution of the ester **14a** (393 mg, 1.78 mmol) in a mixed solvent of MeOH (63 mL) and water (21 mL) was added $LiOH·H_2O$ (560 mg, 13.4 mmol) at 0 °C, and the mixture was stirred overnight at room temperature. HCl (1 N) was added to the mixture, and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with n-hexane−EtOAc (2:1) to give the acid **36** (334 mg, 91% yield) as colorless crystals: mp 112 °C; IR (KBr, cm^{-1}) 3003 (CO_2H), 1709 (CO_2H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (tt, J = 7.8, 7.0 Hz, 2H, 2′-CH_2), 2.14 (s, 3H, CMe), 2.46 (t, J = 7.0 Hz, 2H, CH_2), 2.70 (t, J = 7.8 Hz, 2H, CH_2), 7.28 (d, J = 7.8 Hz, 2H, Ar), 8.04 (d, J = 7.8 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 30.0, 35.0, 42.6, 127.2 (2C), 128.6 (2C), 130.4, 148.1, 172.0, 208.6. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.78; H, 6.81.

***N,N*-Dimethyl-4-(4-oxopentyl)benzamide (37).** To a stirred solution of the acid **36** (752 mg, 3.65 mmol) in a mixed solvent of CH_2Cl_2 (1 mL) and DMF (0.1 mL) was added $SOCl_2$ (0.40 mL, 5.50 mmol) at room temperature, and the mixture was stirred for 2 h at this temperature. Aqueous 40% Me_2NH (1.19 g, 26.3 mmol) solution was added to the mixture over 30 min at 0 °C, and the mixture was stirred overnight at this temperature. Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with EtOAc to give the amide **37** (493 mg, 61% yield) as a colorless oil: IR (KBr, cm^{-1}) 1713 (C=O), 1633 ($CONMe_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (tt, J = 7.5, 7.5 Hz, 2H, 2′-CH_2), 2.12 (s, 3H, CMe), 2.44 (t, J = 7.5 Hz, 2H, CH_2), 2.64 (t, J = 7.5 Hz, 2H, CH_2), 2.99 (br s, 3H, NMe), 3.10 (br s, 3H, NMe), 7.20 (d, J = 8.0 Hz, 2H, Ar), 7.35 (d, J = 8.0 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 30.0, 34.8, 35.4, 39.7, 42.6, 127.3 (2C), 128.4 (2C), 134.0, 143.2, 171.7, 208.7; MS (EI) m/z (rel intens) 233 (M^+, 75), 189 (100); HRMS (EI) m/z calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1428.

General Procedure for Samarium-Mediated Spirocyclization (Workup I). Synthesis of Methyl (1*R,5*R**,8*S**)-1-Hydroxy-1-methylspiro[4.5]dec-6-ene-8-carboxylate (38a) and Its (1*R**,5*R**,8*R**)-Isomer (39a).** A mixture of samarium (82.1 mg, 0.546 mmol) and 1,2-diiodoethane (118 mg, 0.420 mmol) in THF (4 mL) was stirred for 1.5 h. HMPA (0.263 mL, 1.51 mmol) was added to the mixture, and stirring was continued for 10 min. After the mixture was cooled to 0 °C, a solution of the ketone **14a** (18.5 mg, 0.082 mmol) and *i*-PrOH (0.013 mL, 0.168 mmol) in THF (2 mL) was added to the mixture, and the mixture was stirred for 1 h. After the mixture was exposed to air, silica gel was added to the mixture, and the whole was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with n-hexane−EtOAc (4:1), and further purification by flash chromatography over silica gel with $CHCl_3$–acetone (40:1) gave, in order of elution, **38a** (7.5 mg, 40% yield) and **39a** (10.0 mg, 53% yield).

Data for compound **38a** (less polar isomer): colorless oil; IR (KBr, cm^{-1}) 3531 (OH), 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 3H, CMe), 1.25 (br s, 1H, OH), 1.61−2.13 (m, 10H, 5 CH_2), 3.04−3.08 (m, 1H, 8-H), 3.71 (s, 3H, OMe), 5.58 (dd, J = 10.5, 2.5 Hz, 1H, 7-H), 5.72 (d, J = 10.5 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 22.9, 23.9, 27.7, 38.0, 38.9, 41.9, 49.6, 51.9, 82.8, 123.4, 134.9, 174.9; MS (FAB) m/z

231 (MLi^+); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{20}LiO_3$ (MLi^+) 231.1572, found 231.1573.

Data for compound **39a** (more polar isomer): colorless oil; IR (KBr, cm^{-1}) 3544 (OH), 1728 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 3H, CMe), 1.46−2.13 (m, 11H, 5 CH_2 and OH), 3.04−3.07 (m, 1H, 8-H), 3.69 (s, 3H, OMe), 5.61 (d, J = 10.0 Hz, 1H, 6-H), 5.73 (dd, J = 10.0, 4.0 Hz, 1H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.0, 23.6, 26.0, 38.1, 39.0, 40.2, 49.3, 51.8, 82.7, 123.1, 135.5, 174.5; MS (FAB) *m*/*z* 231 (MLi^+); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{20}LiO_3$ (MLi^+) 231.1572, found 231.1573.

General Procedure for Samarium-Mediated Spirocyclization (Workup II). Methyl (1*R,5*S**,8*R**)-1-Hydroxy-1-(phenylmethyl)spiro[4.5]dec-6-ene-8-carboxylate (38c) and Its (1*R**,5*S**,8*S**)-Isomer (39c).** By a procedure identical with that described for the synthesis of **38a** and **39a** from **14a**, the ketone **14c** (49 mg, 0.17 mmol) was treated with samarium (165 mg, 1.10 mmol), diiodoethane (238 mg, 0.85 mmol), *i*-PrOH (0.078 mL, 1.0 mmol), and HMPA (0.53 mL, 3.04 mmol) in THF (10.5 mL). After the mixture was exposed to air, saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with Et_2O. The extract was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (3:1) to give a mixture of the spirocycles **38c** and **39c** (37 mg, 74% yield, **38c**:**39c** = 2:1). Further purification by flash chromatography over silica gel with $CHCl_3$–acetone (80:1) gave, in order of elution, **38c** (24.7 mg, 49% yield) and **39c** (12.3 mg, 25% yield).

Data for compound **38c** (less polar isomer): colorless oil; IR (KBr, cm^{-1}) 3547 (OH), 1736 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.41−2.13 (m, 11H, 5 CH_2 and OH), 2.67 (d, J = 13.3 Hz, 1H, PhC*H*H), 2.75 (d, J = 13.3 Hz, 1H, PhCH*H*), 3.07−3.10 (m, 1H, 8-H), 3.72 (s, 3H, OMe), 5.72 (d, J = 10.3 Hz, 1H, C*H*=CH), 5.80 (d, J = 10.3 Hz, 1H, CH=C*H*), 7.20−7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 24.1, 28.2, 37.6, 38.9, 41.98, 42.02, 50.2, 51.9, 84.1, 123.7, 126.4, 128.3 (2C), 130.3 (2C), 134.8, 138.2, 174.9; MS (FAB) *m*/*z* (rel intens) 323 (MNa^+, 100); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{24}NaO_3$ (MNa^+) 323.1623, found 323.1595.

Data for compound **39c** (more polar isomer): colorless oil; IR (KBr, cm^{-1}) 3543 (OH), 1732 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.36−2.18 (m, 11H, 5 CH_2 and OH), 2.67 (d, J = 13.5 Hz, 1H, PhC*H*H), 2.77 (d, J = 13.5 Hz, 1H, PhCH*H*), 3.07−3.10 (m, 1H, 8-H), 3.70 (s, 3H, OMe), 5.75 (d, J = 10.5 Hz, 1H, 6-H), 5.81 (dd, J = 10.5, 4.3 Hz, 1H, 7-H), 7.21−7.30 (m, 5H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 23.1, 26.0, 37.4, 38.7, 40.2, 42.5, 50.0, 51.8, 84.1, 123.3, 126.3, 128.2 (2C), 130.3 (2C), 135.4, 138.4, 174.4; MS (FAB) *m*/*z* (rel intens) 301 (MH^+, 100); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{25}O_3$ (MH^+) 301.1804, found 301.1800.

Methyl (6*R,7*R**)-7-Hydroxy-7-methylbicyclo[4.4.0]-deca-1(2),4-diene-2-carboxylate (48), Methyl 5-Hydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate, (1*R**,5*R**,6*R**)-6-Hydroxymethyl-1-methylspiro[4.5]dec-7-en-1-ol (71), and (1*R**,5*R**,10*S**)-10-Hydroxymethyl-1-methylspiro[4.5]dec-7-en-1-ol (72).** By a procedure identical with that described for the synthesis of **38a** and **39a** from **14a** (workup I), the ketone **15** (48.7 mg, 0.221 mmol) was converted into an inseparable mixture of **46** and **47** (27.7 mg, 56% yield, **46**:**47** = 7:1) and **48** (3.6 mg, 8% yield). Treatment of **48** (62.1 mg, 0.279 mmol) with *p*-benzoquinone (60.4 mg, 0.558 mmol) in benzene afforded the corresponding aromatized product methyl 5-hydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate. The inseparable mixture of **46** and **47** (49.4 mg, 0.220 mmol) was treated with $LiAlH_4$ (1.0 M in Et_2O; 0.220 mL, 0.220 mmol) in THF (1 mL). Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give, in order of elution, **71** (30.8 mg, 71% yield) and **72** (4.4 mg, 10% yield).

Data for compound **48**: colorless oil; IR (KBr, cm^{-1}) 3413 (OH), 1716 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H, CMe), 1.36−1.88 (m, 6H, 10-C*H*H, 8-CH_2, 9-CH_2 and OH), 2.80−2.98 (m, 3H, 6-H and 3-CH_2), 3.38 (d, J = 13.5 Hz, 1H, 10-CH*H*), 3.74 (s, 3H, OMe), 5.82−5.90 (m, 2H, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 23.8, 28.1, 30.9, 41.5, 51.0, 51.4, 75.6, 121.8, 122.8, 125.1, 145.6, 169.2; MS (FAB) *m*/*z* 223 (MH^+); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{19}O_3$ (MH^+) 223.1334, found 223.1349.

Data for methyl 5-hydroxy-5-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate: colorless oil; IR (KBr, cm^{-1}) 3411 (OH), 1724 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H, CMe), 1.72−2.03 (m, 5H, 2 CH_2 and OH), 3.04−3.08 (m, 2H, 8-CH_2), 3.87 (s, 3H, OMe), 7.26 (dd, J = 7.8, 7.5 Hz, 1H, Ar), 7.71 (dd, J = 7.5, 1.5 Hz, 1H, Ar), 7.80 (dd, J = 7.8, 0.6 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 28.1, 31.1, 39.1, 52.0, 70.9, 125.9, 129.3, 130.0, 130.5, 137.4, 144.3, 168.5; MS (EI) *m*/*z* 220 (M^+, 8), 205 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1120.

Data for compound **71** (less polar isomer): colorless oil; IR (KBr, cm^{-1}) 3255 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.22−1.98 (m, 8H, 4 CH_2), 1.41 (s, 3H, CMe), 2.07−2.21 (m, 2H, 9-CH_2), 2.25−2.28 (m, 1H, 6-H), 2.74 (br, 1H, OH), 3.52 (br, 1H, OH), 3.60−3.68 (m, 2H, 1′-CH_2), 5.57−5.65 (m, 2H, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 20.2, 23.5, 24.5, 32.4, 39.1, 43.0, 47.3, 64.3, 81.2, 127.7, 128.1; MS (FAB) *m*/*z* 219 (MNa^+); HRMS (FAB) *m*/*z* calcd for $C_{12}H_{20}NaO_2$ (MNa^+) 219.1361, found 219.1337.

Data for compound **72** (more polar isomer): colorless oil; IR (KBr, cm^{-1}) 3350 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3H, CMe), 1.53−2.18 (m, 11H, 5 CH_2 and 10-H), 2.46 (br, 1H, OH), 2.58 (br, 1H, OH), 3.60 (dd, J = 11.0, 5.0 Hz, 1H, 1′-C*H*H), 3.99 (dd, J = 11.0, 8.0 Hz, 1H, 1′-CH*H*), 5.70 (ddd, J = 10.0, 3.0, 3.0 Hz, 1H, C=CH), 5.95 (ddd, J = 10.0, 4.0, 2.0 Hz, 1H, C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 21.6, 23.2, 23.8, 39.4, 40.3, 41.0, 50.5, 63.7, 80.9, 127.4, 131.3; MS (FAB) *m*/*z* 219 (MNa^+); HRMS (FAB) *m*/*z* calcd for $C_{12}H_{20}NaO_2$ (MNa^+) 219.1361, found 219.1353.

Methyl (1*R,5*S**,6*R**)-1-Hydroxy-1-methylspiro[4.5]-decane-6-carboxylate (73).** A mixture of alkenes **46** and **47** (19.1 mg, 0.0852 mmol) was subjected to catalytic hydrogenation in MeOH (2 mL) using Pd/C (9.1 mg) under atmospheric pressure of hydrogen at room temperature. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to an oil, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (5:1) to give **73** (16.2 mg, 84% yield, single isomer) as a colorless oil: IR (KBr, cm^{-1}) 3512 (OH), 1713 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07−2.13 (m, 14H, 7 CH_2), 1.12 (s, 3H, CMe), 2.49−2.51 (m, 1H, 6-H), 3.71 (s, 3H, OMe), 4.42 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 21.8, 22.4, 25.1, 25.5, 27.7, 34.4, 38.9, 47.8, 47.9, 51.9, 80.4, 177.9; MS (FAB) *m*/*z* (rel intens) 227 (MH^+, 43), 209 (100); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{23}O_3$ (MH^+) 227.1647, found 227.1654.

General Procedure for the One-Pot Alkylation of the Cyclohexadienyl Anion Intermediates. Synthesis of Methyl 1-Hydroxy-1-methyl-8-(prop-2-enyl)spiro[4.5]deca-6,9-diene-8-carboxylate (68a). By a procedure identical with that described for the synthesis of **38a** and **39a** from **14a**, a solution of SmI_2 in THF−HMPA was prepared from samarium (267 mg, 1.77 mmol) and 1,2-diiodoethane (385 mg, 1.37 mmol). The ketone **14a** (60 mg, 0.273 mmol) and allyl bromide (0.118 mL, 1.37 mmol) were successively added to the solution of SmI_2 at 0 °C. According to the general procedure (workup I), a diastereomixture of the allylated spirocycle **68a** (37 mg, 52% yield, 1.2:1) was obtained.

Data for the less polar isomer: colorless oil; IR (KBr, cm^{-1}) 3535 (OH), 1728 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 3H, CMe), 1.36 (s, 1H, OH), 1.57−2.01 (m, 6H, 3 CH_2), 2.43−2.47 (m, 2H, $CH_2CH=CH_2$), 3.69 (s, 3H, OMe), 5.02−5.07 (m,

2H, CH=CH_2), 5.66 (dd, J = 10.5, 2.5 Hz, 1H, C=CH), 5.70 (ddt, J = 17.5, 10.3, 7.5 Hz, 1H, CH=CH_2), 5.79 (dd, J = 10.5, 2.5 Hz, 1H, C=CH), 5.89 (dd, J = 10.5, 2.5 Hz, 1H, C=CH), 5.95 (dd, J = 10.5, 2.5 Hz, 1H, C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 24.1, 37.9, 38.7, 45.1, 48.5, 51.3, 52.2, 83.4, 118.3, 126.2, 128.6, 130.1, 131.7, 133.3, 174.2; MS (FAB) *m*/*z* (rel intens) 263 (MH^+, 34), 245 (100); HRMS (FAB) *m*/*z* calcd for $C_{16}H_{23}O_3$ (MH^+) 263.1647, found 263.1647.

Data for the more polar isomer: colorless oil; IR (KBr, cm^{-1}) 3539 (OH), 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H, CMe), 1.56−1.98 (m, 7H, 3 CH_2 and OH), 2.46 (d, J = 7.0 Hz, 2H, CH_2CH=CH_2), 3.68 (s, 3H, OMe), 5.05 (d, J = 16.0 Hz, 1H, CH=C*H*H), 5.06 (d, J = 11.0 Hz, 1H, CH=CH*H*), 5.59−5.67 (m, 1H, C*H*=CH_2), 5.65 (d, J = 10.5 Hz, 1H, C=CH), 5.70 (d, J = 10.5 Hz, 1H, C=CH), 5.85 (d, J = 10.5 Hz, 1H, C=CH), 5.88 (d, J = 10.5 Hz, 1H, C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 24.0, 37.6, 38.5, 43.5, 48.6, 51.4, 52.2, 83.9, 118.1, 126.3, 128.4, 130.7, 132.0, 133.2, 174.3; MS (FAB) *m*/*z* (rel intens) 263 (MH^+, 54), 245 (100); HRMS (FAB) *m*/*z* calcd for $C_{16}H_{23}O_3$ (MH^+) 263.1647, found 263.1649.

Methyl (1*R,5*R**)-1-Hydroxy-1-methylspiro[4.5]deca-6,8-diene-8-carboxylate (40a).** By a procedure identical with that described for the synthesis of **38a** and **39a** from **14a**, a solution of SmI_2 in THF−HMPA was prepared from samarium (82 mmol, 0.55 mmol) and 1,2-diiodoethane (141 mg, 0.50 mmol). The ketone **14a** (50 mg, 0.23 mmol) and acetone (0.083 mL, 1.14 mmol) were successively added to the solution of SmI_2 at 0 °C. According to the general procedure (workup II), the diene **40a** (15 mg, 30%) was obtained as a colorless oil: IR (KBr, cm^{-1}) 3523 (OH), 1720 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H, CMe), 1.62−1.96 (m, 7H, 3 CH_2 and OH), 2.35 (dd, J = 19.5, 5.0 Hz, 1H, 10-C*H*H), 2.74 (dd, J = 19.5, 4.5 Hz, 1H, 10-CH*H*), 3.76 (s, 3H, OMe), 5.60 (d, J = 9.8 Hz, 1H, C*H*=CH), 6.35 (d, J = 9.8 Hz, 1H, CH=C*H*), 6.96 (dd, J = 5.0, 4.5 Hz, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 23.3, 29.5, 38.55, 38.60, 48.2, 51.6, 82.8, 120.6, 127.3, 133.2, 137.5, 166.1; MS (EI) *m*/*z* (rel intens) 222 (M^+, 9), 91 (100); HRMS (EI) calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1272.

Methyl 4-(4-Iodopentyl)benzoate (67). NaI (35 mg, 0.242 mmol) was added to a solution of the alcohol **13a** (45 mg, 0.202 mmol) in CH_3CN (0.3 mL) with stirring at room temperature. (TMS)Cl (31 mg, 0.242 mmol) was added to the mixture, and the mixture was stirred at 90 °C until the starting material disappeared on TLC. Water was added to the mixture, and the whole was extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (10:1) to give **67** (35 mg, 52% yield) as a colorless oil: IR (KBr, cm^{-1}) 1720 (C=O), 1281 (C−I); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58−1.65 (m, 1H, 2′-C*H*H), 1.65−1.77 (m, 1H, 2′-CH*H*), 1.80−1.87 (m, 2H, 3-CH_2), 1.89 (d, J = 6.5 Hz, 3H, CMe), 2.65 (ddd, J = 14.0, 8.5, 6.5 Hz, 1H, PhC*H*H), 2.70 (ddd, J = 14.0, 7.0, 6.0 Hz, 1H, PhCH*H*), 3.89 (s, 3H, OMe), 4.13−4.20 (m, 1H, 4′-H), 7.23 (d, J = 8.0 Hz, 2H, Ar), 7.95 (d, J = 8.0 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 29.7, 31.1, 34.9, 42.1, 52.0, 127.9, 128.4 (2C), 129.7 (2C), 147.3, 167.1; MS (FAB) *m*/*z* (rel intens) 333 (MH^+, 100); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{18}IO_2$ (MH^+) 333.0352, found 333.0356.

General Procedure for the DBU-Mediated Alkene Isomerization of Spirocycles for the Determination of the Relative Configurations. Synthesis of Methyl (1*R,5*S**)-1-Hydroxy-1-methylspiro[4.5]dec-7-ene-8-carboxylate (70).** To a stirred solution of the diastereomixture of **38a** and **39a** (44.3 mg, 0.198 mmol; **38a**:**39a** = 1:1.2) in benzene (2 mL) was added DBU (0.030 mL, 0.198 mmol), and the mixture was stirred under reflux for 40 h. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give the isomerized product **70** (30.0 mg, 79% yield) as a single isomer: colorless oil; IR (KBr, cm^{-1}) 3510 (OH), 1713 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 3H, CMe), 1.25 (br s, 1H, OH), 1.43−1.89 (m, 9H, 4 CH_2 and C=CC*H*H), 2.10−2.20 (m, 2H, C=CC*H*H and C=CCH*H*), 2.49−2.54 (m, 1H, C=CCH*H*), 3.74 (s, 3H, OMe), 6.91−6.94 (m, 1H, C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 22.3, 22.5, 25.2, 32.4, 33.2, 39.0, 45.9, 51.5, 82.0, 129.7, 138.7, 167.7; MS (EI) *m*/*z* (rel intens) 224 (M^+, 0.5), 192 (100); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1435.

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Supporting Information Available: Synthetic procedures and characterization for **13b**−**d**, **14b**−**d**, **15**−**22**, **25**−**27**, **29**−**31**, **33b**, **38b,d**−**j**, **39b,d**−**j**, **50**−**54**, **57**−**66**, and **68b,c**, NOE and isomerization experiments for the determination of relative configurations, and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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