JOC Article

Radical Cyclization by Ipso Substitution of the Methoxy Group: Considerable Effect of HMPA on Samarium-Mediated Cyclization

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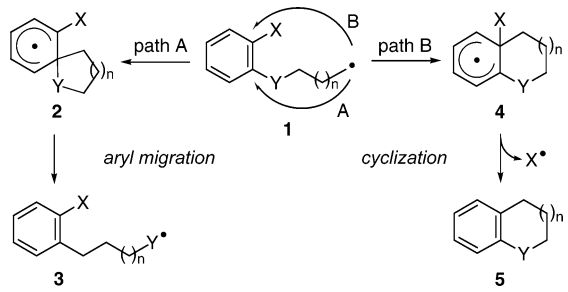
Alkyl radicals generated by treatment of thiocarbamates of conformationally favorable 3-alkyl-3-arylpropan-1-ols with tris(trimethylsilyl)silane and AIBN efficiently undergo intramolecular ipso substitution of the methoxy group, yielding the corresponding cyclized products. In contrast, either conformationally favorable or flexible 1-arylalkan-3- or 4-ones easily cyclize into five- or six-membered condensed rings by treatment with SmI_2 via ketyl radical intermediates. The addition of HMPA as cosolvent dramatically changes the cyclization mode of the SmI_2-induced reaction, and the para-cyclization products are exclusively formed. This "HMPA effect" can be rationalized by the strong chelating ability of HMPA with the samarium atom.

Introduction

Ipso substitution is the usual process occurring in both nucleophilic and electrophilic aromatic substitution including intramolecular reaction. However, intramolecular radical ipso substitution[1] had not received much interest in organic synthesis until recently.[2] Depending on the substitution pattern of the arene ring and regioselectivity of the radical attack, two types of intramolecular radical ipso substitution are possible (Scheme 1): When the radical moiety of **1** attacks the aryl carbon substituted by the Y atom of the side chain (path A) and the Y radical is eliminated from the unstable spirocyclohexadienyl radical intermediate **2**, the rearranged product **3** will be obtained (aryl migration). In contrast, when the intramolecular radical attack takes place at the aryl carbon substituted by another leaving group X (path B), a cyclic compound **5** can be produced by the elimination of the X radical from the cyclohexadienyl radical intermediate **4**. Recently, the intramolecular aryl migration reactions via path A have been widely investigated, and numerous examples of intramolecular aryl migration from sulfur to carbon,[3] oxygen to carbon,[4] silicon to carbon,[5] and other transfers[6,7] are reported, although control of the regioselectivity is sometimes difficult.[8] In contrast, study on the reaction via path B, which provides an attractive synthetic route to bicyclic compounds bearing an aryl group such as **5**, is relatively limited.[9]

SCHEME 1



During the course of our study directed toward the synthesis of macrocarpals,[10] we found a radical ipso substitution of an aromatic methoxy group via path B (X = OMe) mediated by tris(trimethylsilyl)silane (TTMSS)/AIBN (Scheme 2). Compared to the intramolecular radical ipso substitution with a sulfinyl or

(1) For review, see: Traynham, J. G. *Chem. Rev.* **1979**, *79*, 323−330.

(2) For intermolecular radical ipso substitution, see: (a) Traynham, J. G. *Tetrahedron Lett.* **1976**, *26*, 2213−2216. (b) Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Chem. Soc., Chem. Commun.* **1978**, 93−94. (c) Everly, C. R.; Traynham, J. G. *J. Am. Chem. Soc.* **1978**, *100*, 4316−4317. (d) Maiolo, F.; Testaferri, L.; Tiecco, M.; Tingoli, M. *Tetrahedron Lett.* **1981**, *22*, 2023−2024. (e) Moerlein, S. M.; Welch, M. J.; Wolf, A. P. *J. Am. Chem. Soc.* **1983**, *105*, 5418−5428. (f) Inoue, S. *J. Org. Chem.* **1985**, *50*, 1298−1299. (g) Henriquez, R.; Nonhebel, D. C. *Tetrahedron* **1993**, *49*, 6497−6500. (h) Aihara, K.; Urano, Y.; Higuchi, T.; Hirobe, M. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2165−2170. (i) Aboutayab, K.; Caddick, S.; Jenkins, K.; Khan, J. S. *Tetrahedron* **1996**, *52*, 11329−11340. (j) Giraud, L.; Lacôte, E.; Renaud, P. *Helv. Chim. Acta* **1997**, *80*, 2148−2156.

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(4) (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. (d) Harrowven, D. C.; Nunn, M. I. T.; Newman, N. A.; Fenwick, D. R. *Tetrahedron Lett.* **2001**, *42*, 961−964.

(5) (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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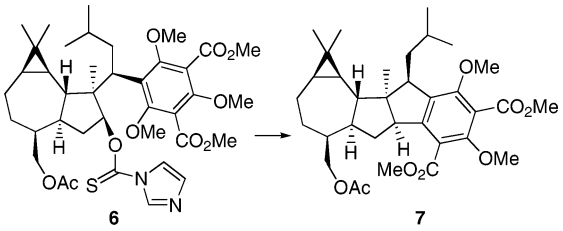
SCHEME 2[a]



[a] Reagents and conditions: TTMSS, AIBN, toluene, sealed tube, 125 °C. Abbreviations: TTMSS = tris(trimethylsilyl)silane.

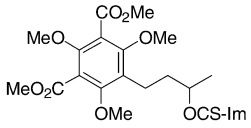
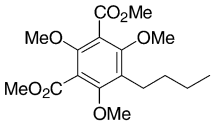
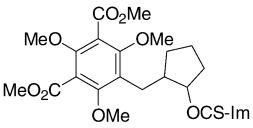
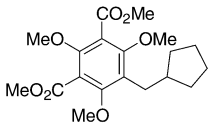
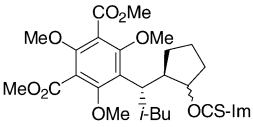
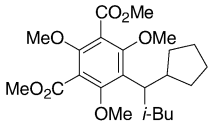
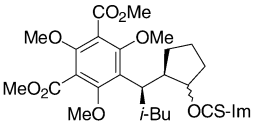
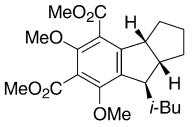
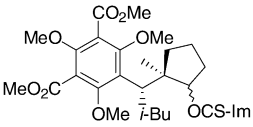
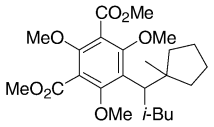
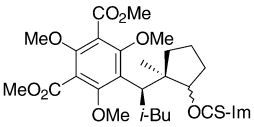
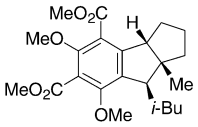
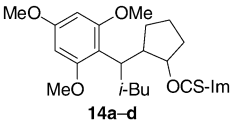
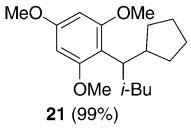
sulfonyl group or halogen atom as a leaving group, the ipso substitution of an alkoxy group is relatively rare.[11] In this paper, we present a full account of our investigation including the samarium(II)-induced cyclization.[12] The scope and limitation of this cyclization and a considerable effect of HMPA on the samarium-mediated cyclization are also presented.

Results and Discussion

Ipso Substitution of Conformationally Favorable Substrates Mediated by TTMSS/AIBN. First, we prepared racemic thiocarbamates **8**−**14** bearing the substituted phenyl group (see the Supporting Information)[13] and investigated the TTMSS/AIBN-mediated cyclization. The results are summarized in Table 1.

Reaction of the thiocarbamates **8** with TTMSS and AIBN in toluene at 125 °C gave only the deoxygenated product **15** in 85% yield (entry 1). Treatment of **9** under identical reaction conditions led to similar results (entry 2). Assuming that the TTMSS-induced ipso substitution shown in Scheme 2 might be highly dependent on the

TABLE 1. TTMSS-Induced Ipso Substitution of an Aromatic Methoxy Group[a,b]

entry	substrate	product (yield)
1	 **8**	 **15** (85%)
2	 **9**	 **16** (88%)
3	 **10a**, **b**	 **17** (99%)
4	 **11a**, **b**	 **18** (56 or 50%) **17** (40 or 48%)
5	 **12a**, **b**	 **19** (99 or 84%)
6	 **13a**, **b**	 **20** (66 or 53%) **19** (31 or 36%)
7	 **14a**–**d**	 **21** (99%)

[a] All reactions were carried out in a sealed tube with TTMSS and AIBN in toluene at 125 °C. [b] We used 10 equiv of TTMSS as the reducing agent. When the reaction of **11** was conducted with 2 equiv of TTMSS, the increased amount of the deoxygenated product **17** was obtained, the reason for which is unclear.

(6) (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.

(7) For related spirocyclization see: (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) Citterio, A.; Sebastiano, R.; Maronati, A.; Santi, R.; Bergamini, F. *J. Chem. Soc., Chem. Commun.* **1994**, 1517−1518. (e) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 5985−5988. (f) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951−8955.

(8) (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) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770. (g) Wang, S.-F.; Chuang, C.-P.; Lee, J.-H.; Liu, S.-T. *Tetrahedron* **1999**, *55*, 2273−2288. (h) Ryokawa, A.; Togo, H. *Tetrahedron* **2001**, *57*, 5915−5921.

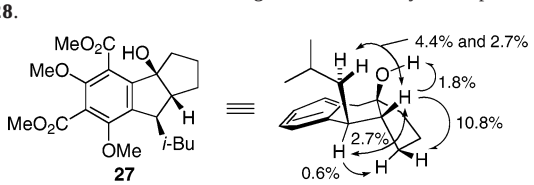
(9) (a) Benati, L.; Montevecchi, P. C.; Tundo, A. *J. Chem. Soc., Chem. Commun.* **1978**, 530−531. (b) Glover, S. A.; Golding, S. L.; Goosen, A.; McCleland, C. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 842−848. (c) Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675−682. (d) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S. *Tetrahedron* **1997**, *53*, 285−298. (e) Aldabbagh, F.; Bowman, W. R. *Tetrahedron* **1999**, *55*, 4109−4122. (f) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **2001**, *42*, 5613−5615.

(10) Tanaka, T.; Mikamiyama, H.; Maeda, K.; Iwata, C. *J. Org. Chem.* **1998**, *63*, 9782−9793.

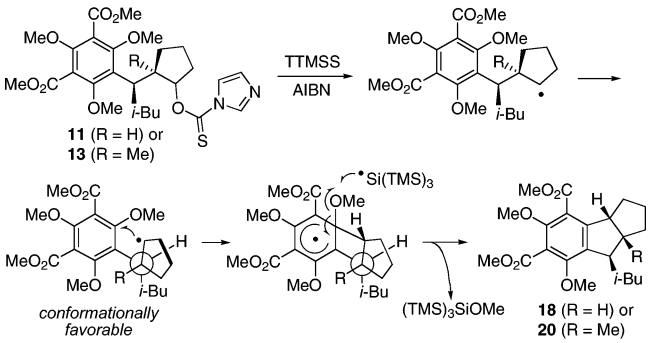
(11) For the radical ipso substitution of an aromatic methoxy group, see refs 2h and 9b,d,f.

(12) For a preliminary communication see: Tanaka, T.; Wakayama, R.; Maeda, S.; Mikamiyama, H.; Maezaki, N.; Ohno, H. *Chem. Commun.* **2000**, 1287−1288.

(13) Determination of stereochemistries of **10**−**13** and **22**−**23** was based on the stereochemical assignments of the cyclized products **27** and **28**.



SCHEME 3



steric nature of the starting thiocarbamates **6**, we investigated the reaction of conformationally restricted substrates **10**−**14** bearing an isobutyl group at the benzylic position. Although both isomers of **10** gave the undesired deoxygenated product **17** quantitatively (entry 3), we were pleased that both isomers of **11** were cyclized into the tricyclic product **18** in 56% and 50% yields, respectively (entry 4), along with the reduction product **17** (40% and 48% yields, respectively). Similarly, while exposure of the methylated substrates **12a** and **12b** to the cyclization conditions led to the undesired reduction (entry 5), the expected ipso substitution proceeded when starting from **13a** or **13b** to afford the cyclized product **20** in 66% or 53% yields, respectively (entry 6). From the result with all four isomers of thiocarbamate **14** as a substrate, it was revealed that the ester functionalities on the arene ring are necessary for the desired cyclization (entry 7).

The conformations of radical intermediates generally have a significant effect on the course of radical reactions. From the results listed in Table 1, the TTMSS-induced cyclization by the radical ipso substitution is limited to conformationally favorable substrates such as **11** and **13** (Scheme 3).[14] However, this drawback of the ipso substitution was overcome by the samarium(II) iodide-mediated cyclization.

Samarium(II)-Mediated Ipso Substitution of the Methoxy Group. In 1977, Kagan reported a convenient method for the preparation of a samarium(II) iodide solution in THF.[15] Since then, both the reduction and carbon−carbon bond formation with samarium(II) reagents have attracted much interest in organic synthesis.[16] In contrast, 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.[17] Reissig and co-workers reported samarium(II)-induced cyclization by the ketyl radical addition onto an appropriately substituted arene ring to form 1,4-cyclohexadiene derivatives.[18] Furthermore, radical ortho cyclization[19] and spirocyclization[20] onto an aromatic ring were reported very recently. However, successful samarium(II)-mediated intramolecular ipso substitution reaction is unknown.[21] We expected that if the strong chelating ability of the samarium atom can assist the approach of the radical species to the arene ring, the above-mentioned radical ipso substitution would be applicable to a wide range of substrates. Accordingly, we next investigated the samarium(II)-mediated ipso substitution of the corresponding ketones.

In our first attempt, we treated the sterically favorable ketone **22** with 3.5 equiv of SmI_2 in THF at room temperature to afford the expected cyclized product **27** in 81% yield (Table 2, entry 1), while the corresponding epimer **23** gave no cyclized product (entry 2).[13,22] Similarly, a diastereomixture of the methylated ketones **24** (1:1) was converted into **28** in 40% yield, along with 46% of the unreacted isomer of **24** (entry 3). Having confirmed that the samarium-induced ipso substitution could proceed when using the sterically favorable substrates, we then turned our attention to the cyclization of sterically flexible substrates. Fortunately, ketones **25** and **26** could be cyclized into **29** and **30**, respectively, by exposure to SmI_2 (entries 4 and 5). It should be clearly noted that, in the TTMSS-induced reaction (Table 1), the corresponding thiocarbamates **8** and **9** yielded no cyclized products.

To reveal a substituent effect on the aromatic ring, we subjected the ketones **31**−**35** to the samarium-mediated cyclization conditions (Table 3). Ketone **31** having no ester functionality was completely inert to the cyclization conditions (entry 1). Similarly, the ipso substitution did not proceed starting from ketones **32a**[23] and **32b** without an ester functionality (entries 2 and 3). In contrast, ketone **32c** bearing one methoxy and one ester group at the appropriate positions cyclized into the desired product **36c** in 50% yield along with 33% of the starting material

(14) According to brief calculations performed by SPARTAN (v 5.1.1) with the MM2 method and the PM3 Hamiltonian, the location of the alkyl radical generated from **11** and **13** is quite close to the reaction site (3.46 and 3.49 Å, respectively) in the most stable conformer. In contrast, in the case of the radical intermediates derived from **10** and **12**, the alkyl radical of the most stable conformers is separated from the reaction site by a relatively long distance (4.61 and 4.58 Å, respectively), which presumably caused undesired reduction instead of cyclization.

(15) (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5−7. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.

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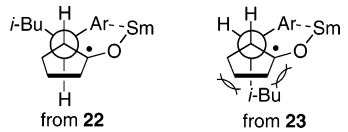
(18) (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **1999**, *38*, 789−791. (b) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267−4277. (c) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290−1292. (d) Gross, S.; Reissig, H.-U. *Synlett* **2002**, 2027−2030.

(19) Kuo, C.-W.; Fang, J.-M. *Synth. Commun.* **2001**, *31*, 877−892.

(20) Ohno, H.; Maeda, S.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316−317.

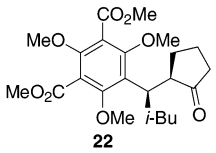
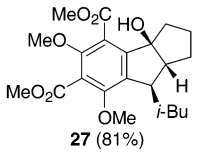
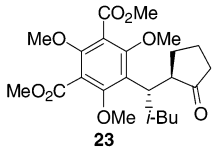
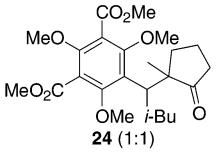
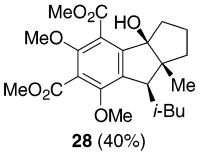
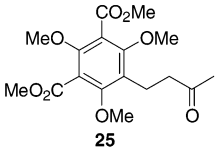
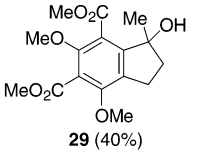
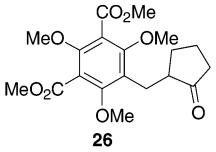
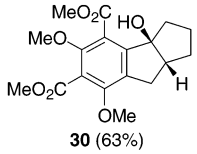
(21) Yanada and co-workers observed a demethoxylative intramolecular coupling of aryl groups as a side reaction, although in low yield (8%): Yanada, R.; Negoro, N.; Okaniwa, M.; Miwa, Y.; Taga, T.; Yanada, K.; Fujita, T. *Synlett* **1999**, 537−540.

(22) Compared to the chelation model (see Scheme 4) derived from **22**, the structure derived from **23** should be destabilized by the unfavorable steric interaction between the cyclopentyl group and the isobutyl group.



(23) Tateiwa, J.; Horiuchi, H.; Hashimoto, K.; Yamauchi, T.; Uemura, S. *J. Org. Chem.* **1994**, *59*, 5901−5904.

TABLE 2. Samarium(II) Iodide-Mediated Ipso Substitution of an Aromatic Methoxy Group[a]

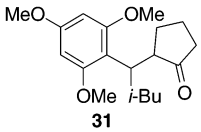
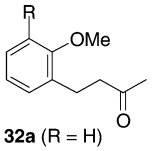
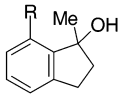
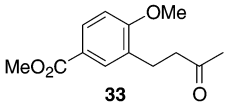
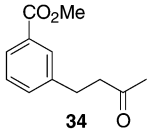
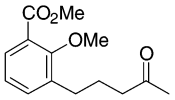
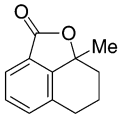
entry	substrate	product (yield)
1	 **22**	 **27** (81%)
2	 **23**	no reaction (75% recovery)
3	 **24** (1:1)	 **28** (40%) recovery (46%)
4	 **25**	 **29** (40%) recovery (33%)
5	 **26**	 **30** (63%) recovery (11%)

[a] All reactions were carried out in THF with SmI_2 (3.5 equiv) at room temperature.

(entry 4). From these results, it was shown that the existence of an electron-withdrawing ester functionality on the arene ring is essential for the present ipso substitution. Interestingly, treatment of ketone **33** bearing an ester group para to the methoxy group with SmI_2 led to recovery of the unchanged starting material (64%) along with isolation of a small amount (22%) of the alcohol as a reduction product (entry 5). As we expected, the cyclization of the demethoxylated substrate **34** did not proceed by treatment with SmI_2, and the starting material was recovered unchanged. Ketone **35** with a three-carbon tether between the carbonyl group and the arene ring afforded tricyclic lactone **37** in high yield (84%) by ipso substitution followed by lactonization.

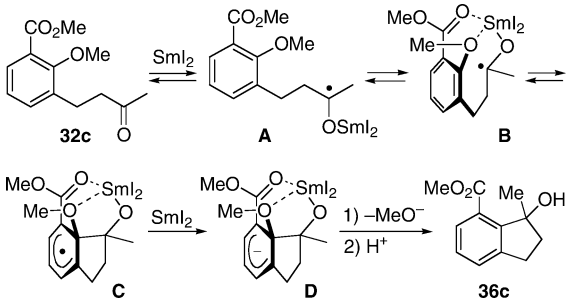
From these observations, the following three points are noted to be extremely important for the present samarium(II)-mediated ipso substitution: (1) ketyl radicals can attack an arene ring starting from either sterically favored or flexible substrates, (2) the arene ring should be substituted by at least one ester group, and (3) the ester group should be located on the ortho position to the methoxy group. One mechanism that could rationalize these three points is shown in Scheme 4. The ketyl radical intermediate **A**, generated by the reaction of ketone **32c** with SmI_2, would be folded like **B** by the chelation of Sm(III) with the oxygen of both the methoxy and the ester groups. Such chelation might attract the ketyl radical close to the reaction site and also activate the aromatic ring, which enables the ketyl radical to attack the aromatic carbon. The resulting dienyl radical **C** was then reduced to the anionic species **D** by single-electron transfer by SmI_2, followed by elimination of the methoxide and hydrolysis to give the rearomatized cyclized product **36c**.[24]

TABLE 3. Effect of the Aromatic Substituents on the Samarium(II) Iodide-Mediated Ipso Substitution[a]

entry	substrate	product (yield)
1	 **31**	no reaction
2	 **32a** (R = H)	 **36a** (0%)
3	**32b** (R = CH_2OAc)	**36b** (0%)
4	**32c** (R = CO_2Me)	**36c** (50%)
5	 **33**	recovery (64%) reduction (22%)
6	 **34**	no reaction
7	 **35**	 **37** (84%)

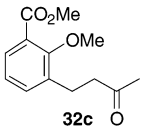
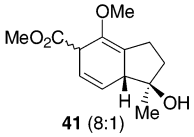
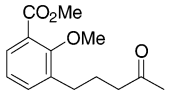
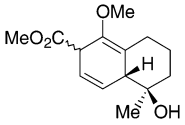
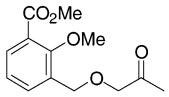
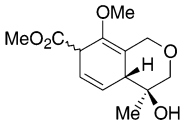
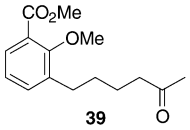
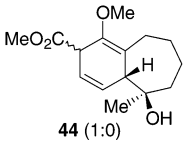
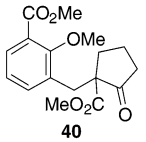
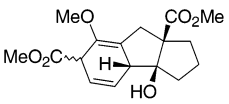
[a] All reactions were carried out in THF with SmI_2 (3.5 equiv) at room temperature.

SCHEME 4



Effect of HMPA on the Samarium(II)-Mediated Substitution Reaction. It is well understood that HMPA can coordinate with samarium and often increases the reducing ability of SmI_2 in a wide range of reactions.[25] If the above SmI_2-mediated cyclization is really accelerated by the chelation of samarium, the reaction course might be significantly changed by the addition of HMPA. Finally, we investigated the effect of HMPA on the SmI_2-mediated cyclization using ketones **32c**, **35**, and **38**−**40**. The results are summarized in Table 4. On treatment of **32c** with SmI_2 in the presence of an excess of HMPA and

TABLE 4. Samarium(II) Iodide-Mediated Cyclization onto Arene Ring in the Presence of HMPA[a]

entry	substrate	product (ratio)	yield
1	 **32c**	 **41** (8:1)	75%
2	 **35**	 **42a**, **b** (1:1)	66%
3	 **38**	 **43a**, **b** (2:1)	33%
4	 **39**	 **44** (1:0)	58%
5	 **40**	 **45** (7:1)	48%

[a] All reactions were carried out in THF with SmI_2 (3.5 equiv), HMPA (18 equiv), and *i*-PrOH (2 equiv) at room temperature.

2 equiv of *i*-PrOH, the cyclization mode was completely changed, yielding **41** bearing the 1,4-cyclohexadienyl moiety in 75% yield as an 8:1 diastereomeric mixture (entry 1). The structure and stereochemistry of **41** were fully characterized by NMR (^{1}H NMR, ^{13}C NMR, C−H COSY, and NOE), IR, HRMS, and chemical transformations.[26] In contrast, the SmI_2/HMPA-mediated cyclization of **32c** in the absence of any protic source afforded the recovered starting material **32c** with only a trace amount of the cyclized product **41**. These results clearly demonstrate that the protonation of the cyclohexadienyl anion intermediate by *i*-PrOH might shift the equilibrium toward the cyclized product. Similarly, ketones **35** and **38** were cyclized into six-membered rings **42** and **43**, respectively, although somewhat decreased diastereoselectivities were observed (entries 2 and 3).[27] Interestingly, ketone **39** bearing a four-carbon tether between the aryl and carbonyl groups promoted seven-membered-ring formation under the identical reaction conditions (entry 4). Furthermore, construction of a tricyclic skeleton is possible by using a cyclic ketone such as **40** as the starting material (entry 5).

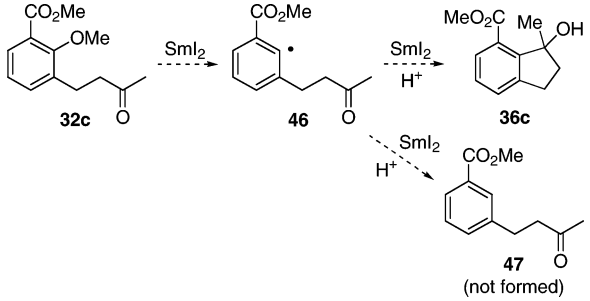
These results are comparable to those reported by Reissig, in that 1,4-cyclohexadiene derivatives were obtained by treatment of phenylpentan-2-ones bearing an ethynyl, methoxy, or amide functionality on the arene ring with SmI_2 in the presence of HMPA and *t*-BuOH.[18] However, our study reveals that the ester group on the arene ring can also promote a similar type of cyclization[28] and that the SmI_2/HMPA-mediated cyclization onto an arene ring can facilitate the synthesis of seven-membered rings as well as tricyclic compounds.

The "HMPA effect" is extremely interesting in that the para cyclization to the ester group is promoted by the addition of HMPA while the ipso substitution of the methoxy group predominates in the absence of HMPA (Tables 2, 3, and 4). Considering the ability of HMPA to coordinate with samarium, we speculate that the effect of HMPA on the cyclization is as follows: the chelation of Sm−O as depicted in structure **B** (Scheme 4) is effectively inhibited by HMPA, making the ketyl radical conformationally free, which enabled the radical species to attack at the most reactive carbon.[29]

Conclusion

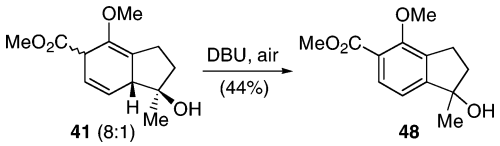
In conclusion, we have developed a novel cyclization reaction by radical ipso substitution of an aromatic

(24) We cannot rule out another mechanism through reduction of the electron-deficient aromatic ring, expulsion of the methoxy group, and attack of the resulting arene radical **46** on the carbonyl group (see below). However, the mechanistic pathway shown in Scheme 4 better explains both the experimental result that no demetoxylative reduction products such as **47** was obtained and that the ketone **33** is completely inert to the samarium-mediated cyclization conditions (Table 3, entry 5).



(25) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett*, **1987**, 1485−1486. (b) Shabangi, M.; Flowers, R. A., II *Tetrahedron Lett*. **1997**, *38*, 1137−1140. (c) 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. (d) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382−5390. (e) Knettle, B. W.; Flowers, R. A., II *Org. Lett.* **2001**, *3*, 2321−2324. (f) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2002**, *124*, 6895−6899.

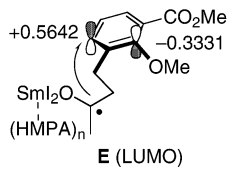
(26) Treatment of the diastereomixture **41** with DBU in the presence of air yielded the corresponding aromatized compound **48**.



(27) The ketone **33** is less reactive to the SmI_2/HMPA-mediated cyclization conditions. Treatment of **33** with SmI_2 and HMPA in the presence of *i*-PrOH gave an inseparable mixture of the recovered starting material and an unidentified cyclized product.

(28) In 2001, Fang and Kuo reported a similar radical cyclization onto an aryl group substituted by a formyl or an ester group to form rearomatized products instead of the 1,4-cyclohexadiene derivatives, see ref 19.

(29) According to a brief MO calculation performed by SPARTAN (v 5.1.1) with the MM2 method and the PM3 Hamiltonian, the electron density of the carbon para to the ester group is estimated to be higher than that bearing the methoxy group in the LUMO of the intermediate **E**.



E (LUMO)

methoxy group. While reaction of alkyl radicals generated by treatment of thiocarbamates of 3-alkyl-3-arylpropan-1-ols with TTMSS and AIBN is highly dependent on the structure of the starting materials, SmI_2-mediated cyclization of 1-arylalkan-3- or 4-ones was found to be applicable to a wide range of substrates. When the SmI_2-induced cyclization was carried out in the presence of HMPA and *i*-PrOH, the cyclization mode was dramatically changed, yielding 1,4-cyclohexadiene derivatives including a seven-membered ring and a tricyclic compound.

Experimental Section

General Procedure for the TTMSS-Mediated Ipso Substitution: Synthesis of Dimethyl (3a*R,8*R**,8a*S**)-8-Isobutyl-5,7-dimethoxy-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene-4,6-dicarboxylate (18) and Dimethyl 5-(1-Cyclopentyl-3-methylbutyl)-2,4,6-trimethoxybenzene-1,3-dicarboxylate (17) (Table 1, entry 4).** A mixture of the thiocarbamate **11b** (25.0 mg, 0.0456 mmol), $(TMS)_3SiH$ (0.137 mL, 0.510 mmol), and AIBN (2.0 mg, 0.0114 mmol) in dry toluene (5.0 mL) was heated at 125 °C for 24 h in a sealed tube. The mixture was concentrated under reduced pressure to leave an oily residue, which was purified by preparative TLC (PTLC) with *n*-hexane−EtOAc (2:1) to give the cyclized product **18** (8.9 mg, 50%) and deoxygenated product **17** (9.2 mg, 48%).

Compound 18: colorless oil; IR (KBr) 1736 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3H, CMe), 0.99 (d, J = 7.0 Hz, 3H, CMe), 1.18−1.34 (m, 2H), 1.34−1.44 (m, 1H), 1.46−1.52 (m, 1H), 1.60−1.65 (m, 2H), 1.72−1.80 (m, 1H), 1.87−1.94 (m, 1H), 1.98−2.05 (m, 1H), 2.48−2.53 (m, 1H), 3.05 (ddd, J = 11.0, 2.4, 2.4 Hz, 1H), 3.80−4.00 (m, 1H), 3.81 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.91 (s, 3H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 24.0, 26.1, 26.4, 33.5, 34.9, 44.7, 47.5, 48.8, 49.1, 52.1, 52.5, 60.7, 63.5, 119.0, 121.0, 135.1, 152.0, 155.3, 156.4, 166.7, 167.0; MS (EI) *m*/*z* (%) 390 (M^+, 27), 333 (100); HRMS (EI) calcd for $C_{22}H_{30}O_6$ (M^+) 390.3042, found 390.2042.

Compound 17: colorless prisms; IR (KBr) 1734 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, J = 6.4 Hz, 3H, CMe), 0.88 (d, J = 6.4 Hz, 3H, CMe), 1.14−1.62 (m, 9H), 1.74 (ddd, J = 13.4, 10.7, 3.7 Hz, 1H), 1.90−2.02 (m, 1H), 2.23−2.37 (m, 1H), 2.91 (td, J = 10.7, 4.3 Hz, 1H), 3.75 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.89 (s, 6H, 2 × OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1, 24.1, 25.0, 25.3, 26.3, 32.2, 32.9, 40.8, 43.3, 44.1, 52.6, 52.7, 61.0, 62.3, 63.7, 117.3, 117.4, 128.0, 154.5, 158.1, 159.2, 166.7 (2C); MS (EI) *m*/*z* (%) 423 (MH^+, 3), 297 (100); HRMS (EI) calcd for $C_{23}H_{34}O_7$ (M^+) 422.2319, found 422.2305.

Dimethyl (3a*R,8*R**,8a*S**)-8-Isobutyl-5,7-dimethoxy-8a-methyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene-4,6-dicarboxylate (20) and Dimethyl 2,4,6-Trimethoxy-5-[3-methyl-1-(1-methylcyclopentyl)butyl]benzene-1,3-dicarboxylate (19) (Table 1, entry 6).** By a procedure identical with that described for the synthesis of **18**, thiocarbamate **13a** (45.6 mg, 0.081 mmol) was converted into **20** (21.6 mg, 66% yield) and **19** (11.0 mg, 31% yield). Similarly, thiocarbamate **13b** (25.3 mg, 0.045 mmol) was converted into **20** (13.3 mg, 53% yield) and **19** (7 mg, 36% yield).

Compound 20: colorless oil; IR (KBr) 1736 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 3H, CMe), 0.96 (d, J = 6.7 Hz, 3H, CMe), 1.31 (s, 3H, CMe), 1.41 (ddd, J = 13.5, 7.5, 5.5 Hz, 1H), 1.47−1.59 (m, 5H), 1.67−1.72 (m, 2H), 2.08−2.37 (m, 1H), 3.08 (dd, J = 7.5, 4.5 Hz, 1H), 3.35 (dd, J = 9.5, 4.5 Hz, 1H), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.92 (s, 3H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0, 22.4, 23.3, 24.9, 26.4, 31.9, 41.1, 41.6, 48.8, 52.1, 52.5, 54.0, 56.4, 61.1, 63.5, 119.3, 121.2, 135.9, 151.8, 155.7, 156.1, 166.8, 166.9; MS (EI) *m*/*z* (%) 404 (M^+, 14), 347 (100); HRMS (EI) calcd for $C_{23}H_{32}O_6$ (M^+) 404.2199, found 404.2199.

Compound 19: colorless oil; IR (KBr) 1736 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 3H, CMe), 0.85 (d, J = 6.7 Hz, 3H, CMe), 0.87 (d, J = 6.7 Hz, 3H, CMe), 1.11−1.15 (m, 1H), 1.20−1.38 (m, 2H), 1.48−1.64 (m, 7H), 1.99−2.05 (m, 1H), 3.27 (dd, J = 11.6, 3.7 Hz, 1H), 3.74 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.92 (s, 6H, 2 × OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9, 23.7, 24.3, 24.6, 25.0, 26.4, 38.0, 38.2, 39.1, 43.2, 46.2, 52.6, 52.7, 60.0, 62.0, 63.9, 116.5, 116.6, 125.7, 154.6, 159.0, 159.3, 166.8, 167.0; MS (EI) *m*/*z* (%) 436 (M^+, 1.8), 297 (100); HRMS (EI) calcd for $C_{24}H_{36}O_7$ (M^+) 436.2462, found 436.2461.

General Procedure for the Samarium(II) Iodide-Mediated Ipso Substitution: Synthesis of Dimethyl (3a*R,8*S**,8a*S**)-3a-Hydroxy-8-isobutyl-5,7-dimethoxy-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene-4,6-dicarboxylate (27) (Table 2, entry 1).** Samarium (82.7 mg, 0.55 mmol) and 1,2-diiodoethane (140.9 mg, 0.50 mmol) were mixed in freshly distilled THF (5.0 mL) under argon and stirred for 1.5 h at room temperature. The resulting dark-blue solution (4.04 mL, 0.404 mmol) was added to a solution of ketone **22** (50.4 mg, 0.12 mmol) in THF (1.0 mL) under argon at room temperature and the mixture was stirred for 12 h. Saturated NH_4Cl and SiO_2 were 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) to give **27** (38.2 mg, 81% yield) as a colorless oil: IR (KBr) 3469 cm^{-1} (br, OH), 1736 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.7 Hz, 3H, CMe), 0.99 (d, J = 6.7 Hz, 3H, CMe), 1.18−1.27 (m, 1H, 1-C*H*H), 1.42 (ddd, J = 11.6, 11.6, 3.7 Hz, 1H, 1′-C*H*H), 1.66−1.83 (m, 5H, 1′-CH*H*, 2′-H, 2-CH_2, and 3-C*H*H), 2.13−2.19 (m, 1H, 1-CH*H*), 2.04−2.09 (m, 1H, 3-CH*H*), 2.41 (ddd, J = 8.5, 8.5, 1.8 Hz, 1H, 8a-H), 2.92 (ddd, J = 11.6, 1.8, 1.8 Hz, 1H, 8-H), 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.97 (s, 3H, OMe), 4.42 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.3, 23.9, 26.1, 26.3, 34.7, 41.3, 44.7, 45.9, 52.6, 52.8, 57.3, 60.5, 63.6, 92.3, 117.1, 122.3, 135.5, 151.8, 156.4, 157.3, 166.4, 168.8; MS (EI) *m*/*z* (%) 407 (MH^+, 22), 318 (100); HRMS (EI) calcd for $C_{22}H_{30}O_7$ (M^+) 406.1991, found 406.1993.

Dimethyl (3a*R,8*S**,8a*S**)-3a-Hydroxy-8-isobutyl-5,7-dimethoxy-8a-methyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene-4,6-dicarboxylate (28) (Table 2, entry 3).** By a procedure identical with that described for the synthesis of **27**, a diastereomixture of ketones **24** (1:1, 84.0 mg, 0.186 mmol) was converted into **28** (31.7 mg, 40% yield) and recovered ketones **24** (38.8 mg, 46%): colorless oil; IR (KBr) 3512 (br, OH), 1736 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.5 Hz, 3H, CMe), 1.02 (d, J = 6.5 Hz, 3H, CMe), 1.25 (s, 3H, CMe), 1.41−1.59 (m, 3H, 1′-C*H*H, 2-C*H*H, and 3-C*H*H), 1.62−1.68 (m, 1H, 2′-H), 1.80−1.89 (m, 2H, 1-CH*H* and 2-CH*H*), 1.92−1.99 (m, 2H, 1-CH*H* and 1′-CH*H*), 2.06 (ddd, J = 13.5, 9.5, 5.0 Hz, 1H, 3-CH*H*), 3.15 (dd, J = 9.1, 3.7 Hz, 1H, 8-H), 3.78 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.88 (br s, 1H, OH), 3.93 (s, 3H, OMe), 3.95 (s, 3H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 22.2, 23.2, 23.9, 26.7, 35.0, 38.1, 40.1, 48.7, 52.6, 52.9, 56.2, 60.8, 63.8, 91.0, 118.3, 123.3, 134.6, 151.7, 156.1, 156.6, 166.4, 168.6; MS (EI) *m*/*z* (%) 420 (M^+, 29), 331 (100); HRMS (EI) calcd for $C_{23}H_{32}O_7$ (M^+) 420.2143, found 420.2148.

Dimethyl 3-Hydroxy-5,7-dimethoxy-3-methyl-2,3-dihydro-1*H*-indene-4,6-dicarboxylate (29) (Table 2, entry 4). By a procedure identical with that described for the synthesis of **27**, ketone **25** (52.0 mg, 0.147 mmol) was converted into **29** (19.0 mg, 40% yield) and recovered ketone **25** (17.1 mg, 33%): colorless oil; IR (KBr) 3504 (br, OH), 1734 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.54 (s, 3H, CMe), 2.19 (ddd, J = 12.2, 7.9, 3.7 Hz, 1H, 2-C*H*H), 2.25 (ddd, J = 12.2, 7.9, 7.9 Hz, 1H, 2-CH*H*), 2.79 (ddd, J = 16.5, 7.9, 7.9 Hz, 1H, 1-C*H*H), 3.02 (ddd, J = 16.5, 8.5, 3.7 Hz, 1H, 1-CH*H*), 3.62 (s, 1H, OH), 3.81 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.96 (s, 3H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.4, 27.1, 42.1, 52.6,

52.7, 60.5, 63.8, 81.8, 117.7, 121.7, 129.8, 151.9, 155.4, 156.4, 166.3, 168.3; MS (EI) *m*/*z* (%) 324 (M^+, 6), 277 (100); HRMS (EI) calcd for $C_{16}H_{20}O_7$ (M^+) 324.1224, found 324.1209.

Dimethyl (3a*R,8a*S**)-3a-Hydroxy-5,7-dimethoxy-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene-4,6-dicarboxylate (30) (Table 2, entry 5).** By a procedure identical with that described for the synthesis of **27**, ketone **26** (47.5 mg, 0.131 mmol) was converted into **30** (27.5 mg, 63% yield) and recovered ketone **26** (5.0 mg, 11%): colorless oil; IR (KBr) 3487 (br, OH), 1736 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.17−1.29 (m, 1H), 1.53−1.67 (m, 1H), 1.75−1.88 (m, 2H), 2.01−2.17 (m, 2H), 2.55 (dd, J = 16.2, 3.6 Hz, 1H, 8-C*H*H), 2.71 (m, 1H), 3.28 (dd, J = 16.2, 8.7 Hz, 1H, 8-CH*H*), 3.76 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.41 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.2, 34.1, 34.3, 41.2, 51.1, 52.6, 52.8, 60.2, 63.7, 93.2, 116.9, 121.9, 130.6, 152.3, 155.9, 157.2, 166.3, 168.7; MS (EI) *m*/*z* (%) 350 (M^+, 21), 289 (100); HRMS (EI) calcd for $C_{18}H_{22}O_7$ (M^+) 350.1365, found 350.1365.

Methyl 3-Hydroxy-3-methyl-2,3-dihydro-1*H*-indene-4-carboxylate (36c) (Table 3, entry 4). By a procedure identical with that described for the synthesis of **27**, ketone **32c** (49.0 mg, 0.207 mmol) was converted into **36c** (21.4 mg, 50% yield) and recovered ketone **32c** (16.2 mg, 33%): colorless oil; IR (KBr) 3456 (br, OH), 1700 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.54 (s, 3H, CMe), 2.22 (ddd, J = 12.5, 8.0, 1.8 Hz, 1H, 2-C*H*H), 2.26−2.32 (m, 1H, 2-CH*H*), 2.79−2.86 (m, 1H, 1-C*H*H), 2.95 (ddd, J = 16.5, 9.2, 1.8 Hz, 1H, 1-CH*H*), 3.93 (s, 3H, OMe), 5.81 (s, 1H, OH), 7.26 (dd, J = 7.9, 7.3 Hz, 1H, Ar), 7.38 (dd, J = 7.3 Hz, 1H, Ar), 7.88 (d, J = 7.9 Hz, 1H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.9, 29.4, 41.4, 52.1, 81.8, 125.3, 127.6, 129.8, 130.3, 143.9, 151.3, 168.8; MS (EI) *m*/*z* (%) 207 (MH^+, 10), 191 (100); HRMS (FAB) calcd for $C_{12}H_{15}O_3$ (MH^+) 207.1022, found 207.1017.

8a-Methyl-6,7,8,8a-tetrahydronaphtho[1,8-*bc*]furan-2-one (37) (Table 3, entry 7). By a procedure identical with that described for the synthesis of **27**, ketone **35** (48.6 mg, 0.194 mmol) was converted into **37** (30.6 mg, 84% yield): colorless oil; IR (KBr) 1763 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47−1.55 (m, 1H, 8-C*H*H), 1.59 (s, 3H, CMe), 2.01−2.12 (m, 2H, 7-CH_2), 2.32 (ddd, J = 12.2, 5.8, 3.7 Hz, 1H, 8-CH*H*), 2.78 (ddd, J = 17.4, 8.2, 6.1 Hz, 1H, 6-C*H*H), 2.98 (ddd, J = 17.4, 7.6, 6.4 Hz, 1H, 6-CH*H*), 7.35 (d, J = 7.3 Hz, 1H, Ar), 7.41 (t, J = 7.3 Hz, 1H, Ar), 7.63 (d, J = 7.3 Hz, 1H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5, 23.3, 24.6, 32.2, 83.5, 123.0, 123.9, 129.6, 132.0, 134.0, 153.4, 170.0; MS (EI) *m*/*z* (%) 188 (M^+, 10), 173 (100); HRMS (EI) calcd for $C_{12}H_{12}O_2$ (M^+) 188.0837, found 188.0837.

General Procedure for the Samarium(II) Iodide-Mediated Cyclization in the Presence of HMPA: Synthesis of Methyl (1*R,7a*R**)-1-Hydroxy-4-methoxy-1-methyl-2,3,5,7a-tetrahydro-1*H*-indene-5-carboxylate (41) (Table 4, entry 1).** Samarium (182.4 mg, 1.20 mmol) and 1,2-diiodoethane (307.8 mg, 1.09 mmol) were mixed in freshly distilled THF (6.54 mL) under argon and stirred for 1.5 h at room temperature. To the resulting dark-blue solution was added HMPA (0.684 mL, 3.91 mmol) and the mixture was stirred for 10 min at room temperature. To the stirred mixture was added a solution of ketone **32c** (51.2 mg, 0.217 mmol) and *i*-PrOH (33 μL, 0.434 mmol) in THF (5.0 mL) over 30 min at room temperature. After the mixture was stirred for 2 h, saturated NH_4Cl (2.0 mL) and SiO_2 (2.0 g) were added to the mixture. The whole was concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel with *n*-hexane−EtOAc (2:1) to give **41** (38.7 mg, 75% yield) as a 8:1 diastereomixture: colorless oil; IR (KBr) 3479 (OH), 1736 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 3H, CMe), 1.78−1.90 (m, 3H, 2-CH_2 and OH), 2.37 (ddd, J = 17.1, 9.2, 9.2 Hz, 1H, 3-C*H*H), 2.58 (ddd, J = 17.1, 10.4, 1.8 Hz, 1H, 3-CH*H*), 3.13−3.15 (m, 1H, 7a-H), 3.68 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.82−3.83 (m, 1H, 5-H), 5.82 (ddd, J = 9.2, 4.3, 2.4 Hz, 1H, 7-H), 5.94 (ddd, J = 9.2, 1.8, 1.8 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 23.2, 39.3, 46.6, 52.3, 52.6, 58.1, 78.9, 118.9, 124.0, 127.1, 144.0, 172.1; MS (EI) *m*/*z* (%) 238 (M^+, 3), 121 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_4$ (MH^+) 239.1283, found 239.1273.

Methyl (4a*R,5*S**)-5-Hydroxy-1-methoxy-5-methyl-2,4a,5,6,7,8-hexahydronaphthalene-2-carboxylates (42a and 42b) (Table 4, entry 2).** By a procedure identical with that described for the synthesis of **42**, ketone **35** (51.3 mg, 0.217 mmol) was converted into **42a** (17.1 mg, 33% yield) and **42b** (17.1 mg, 33% yield).

Compound 42a: colorless oil; IR (KBr) 3446 (OH), 1736 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3H, CMe), 1.29−1.37 (m, 1H, 7-C*H*H), 1.42 (br s, 1H, OH), 1.52−1.69 (m, 2H, 6-C*H*H and 8-C*H*H), 1.72−1.82 (m, 2H, 6-CH*H* and 7-CH*H*), 2.82−2.85 (m, 1H, 4a-H), 2.91 (ddd, J = 13.7, 1.8, 1.8 Hz, 1H, 8-CH*H*), 3.52 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.93−3.98 (m, 1H, 2-H), 5.74 (ddd, J = 10.1, 3.3, 1.8 Hz, 1H, 4-H), 6.01 (ddd, J = 10.1, 2.4, 2.4 Hz, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 23.5, 25.0, 41.8, 44.0, 50.3, 52.5, 58.7, 74.3, 121.6, 122.7, 127.2, 143.7, 172.0; MS (FAB) *m*/*z* (%) 253 (MH^+, 74), 235 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_4$ (MH^+) 253.1440, found 253.1446.

Compound 42b: colorless oil; IR (KBr) 3498 (OH), 1738 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H, CMe), 1.35−1.64 (m, 4H, 6-C*H*H, 7-CH_2, and OH), 1.70−1.83 (m, 2H, 6-CH*H* and 8-C*H*H), 2.74−2.77 (m, 1H, 8-CH*H*), 2.90−2.96 (m, 1H, 4a-H), 3.50 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.96 (ddd, J = 8.9, 4.0, 2.1 Hz, 1H, 2-H), 5.75 (ddd, J = 10.1, 4.0, 2.1 Hz, 1H, 4-H), 5.99 (ddd, J = 10.1, 3.7, 2.1 Hz, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 23.4, 25.1, 41.9, 44.1, 50.8, 52.3, 58.0, 74.7, 121.5, 122.8, 127.2, 143.3, 171.9; MS (EI) *m*/*z* (%) 252 (M^+, 12), 85 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_4$ (MH^+) 253.1440, found 253.1446.

Methyl (4*R,4a*S**)-4-Hydroxy-8-methoxy-4-methyl-3,4,4a,7-tetrahydro-1*H*-2-benzopyran-7-carboxylates (43a and 43b) (Table 4, entry 3).** By a procedure identical with that described for the synthesis of **41**, ketone **38** (48.2 mg, 0.217 mmol) was converted into an inseparable diastereomixture of **43a** and **43b** (15.8 mg, 33% yield, 2:1): colorless oil; IR (KBr) 3521 (OH), 1738 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) major isomer δ 1.07 (s, 3H, CMe), 1.54 (br s, 1H, OH), 2.96 (d, J = 6.7 Hz, 1H, CH), 3.29 (br s, 1H, CH), 3.51 (s, 3H, OMe), 3.55 (d, J = 6.7 Hz, 1H, CH), 3.66 (s, 3H, OMe), 3.93−3.98 (m, 1H, CH), 4.78 (d, J = 12.8 Hz, 1H, CH), 5.74−5.78 (m, 1H, C*H*=CH), 5.90−5.97 (m, 1H, CH=C*H*), minor isomer δ 1.15 (s, 3H, CMe), 1.54 (br s, 1H, OH), 2.88 (d, J = 7.0 Hz, 1H, CH), 3.25 (br s, 1H, CH), 3.46 (s, 3H, OMe), 3.57 (d, J = 7.0 Hz, 1H, CH), 3.66 (s, 3H, OMe), 3.93−3.98 (m, 1H, CH), 4.80 (d, J = 12.8 Hz, 1H, CH), 5.71−5.76 (m, 1H, C*H*=CH), 5.90−5.97 (m, 1H, CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer δ 20.9, 43.3, 47.8, 52.6, 58.0, 64.4, 71.3, 77.7, 116.3, 122.9, 126.0, 144.9, 171.4, minor isomer δ 21.3, 43.9, 48.5, 52.5, 58.3, 64.3, 72.0, 77.4, 116.3, 123.2, 125.7, 144.9, 171.3; MS (EI) *m*/*z* (%) 266 (M^+, 8), 121 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_5$ (MH^+) 255.1233, found 255.1242.

Methyl (4a*R,5*S**)-5-Hydroxy-1-methoxy-5-methyl-4a,5,6,7,8,9-hexahydro-2*H*-benzocycloheptene-2-carboxylate (44) (Table 4, entry 4).** By a procedure identical with that described for the synthesis of **41**, ketone **39** (50.0 mg, 0.189 mmol) was converted into **44** (29.0 mg, 58% yield): colorless oil; IR (KBr) 3489 (OH), 1738 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H, CMe), 1.36−1.46 (m, 2H), 1.58−1.81 (m, 5H), 2.12−2.22 (m, 1H, 9-C*H*H), 2.67 (ddd, J = 15.9, 8.7, 5.1 Hz, 1H, 9-CH*H*), 3.06 (dd, J = 4.5, 4.2 Hz, 1H, 4a-H), 3.55 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.98−4.02 (m, 1H, 2-H), 5.83 (ddd, J = 9.9, 4.5, 0.9 Hz, 1H, C*H*=CH), 6.01 (ddd, J = 9.9, 4.2, 1.5 Hz, 1H, CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.9, 24.4, 27.8, 43.5, 44.2, 51.2, 52.2, 56.9, 76.9, 120.7, 122.5, 129.8, 145.6, 171.7; MS (EI) *m*/*z* (%) 266 (M^+, 8), 121 (100); HRMS (FAB) calcd for $C_{15}H_{22}O_4Na$ (MNa^+) 289.1416, found 289.1413.

Dimethyl (3a*R,3b*S**,8a*S**)-3a-Hydroxy-7-methoxy-2,3,3a,3b,6,8-hexahydro-1*H*-cyclopenta[*a*]indene-6,8a-dicarboxylate (45) (Table 4, entry 5).** By a procedure identical with that described for the synthesis of **41**, ketone **40** (39.8 mg, 0.124 mmol) was converted into an inseparable mixture of **45** (19.4 mg, 48% yield, 7:1): colorless oil; IR (KBr) 3510 (OH), 1732 cm^{-1} (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46−1.65 (m, 5H), 1.68−1.78 (m, 1H), 2.26−2.41 (m, 1H), 2.47 (d, J = 16.8 Hz, 1H, 8-C*H*H), 3.05 (d, J = 16.8 Hz, 1H, 8-CH*H*), 3.42 (d, J = 7.2 Hz, 1H), 3.64 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.83−3.85 (m, 1H), 5.80 (ddd, J = 9.4, 4.6, 2.4 Hz, 1H, C*H*═CH), 5.96 (ddd, J = 9.4, 2.4, 2.4 Hz, 1H, CH═C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 36.0, 37.1, 37.5, 46.2, 51.8, 52.2, 58.7, 60.4, 91.3, 117.5, 123.6, 127.3, 143.7, 171.8, 176.8, 184.1; MS (EI) *m*/*z* (%) 322 (M^+, 0.2), 121 (100); HRMS (FAB) calcd for $C_{17}H_{23}O_6$ (MH^+) 323.1495, found 323.1489.

Methyl 1-Hydroxy-4-methoxy-1-methyl-2,3-dihydro-1*H*-indene-5-carboxylate (48). To a stirred solution of 1,4-cyclohexadiene **41** (21.1 mg, 0.089 mmol) in benzene (5.0 mL) was added DBU (6.62 mL, 0.044 mmol) and the mixture was heated under reflux for 12 h in the presence of air. The mixture was neutralized with 5% HCl at 0 °C 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 (1:1) to give the aromatized compound **48** (9.2 mg, 44% yield) as a colorless oil: IR (KBr) 3456 (br, OH), 1700 cm^{-1} (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H, CMe), 1.95 (br s, 1H, OH), 2.14−2.29 (m, 2H, 2-CH_2), 2.84 (ddd, J = 15.9, 7.5, 7.5 Hz, 1H, 3-C*H*H), 3.05 (ddd, J = 15.9, 7.8, 4.8 Hz, 1H, 3-CH*H*), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.09 (d, J = 7.8 Hz, 1H, Ar), 7.66 (d, J = 7.8 Hz, 1H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.4, 27.2, 42.2, 52.2, 61.0, 81.8, 117.4, 123.7, 130.9, 135.6, 155.0, 156.4, 166.8; MS (EI) *m*/*z* (%) 236 (M^+, 18), 221 (100); HRMS (FAB) calcd for $C_{13}H_{17}O_4$ (MH^+) 237.1127, found 237.1122.

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Supporting Information Available: Synthetic procedures and characterization for **8**−**16**, **21**−**26**, **31**−**35**, and **38**−**40**; NMR spectra for **11a**, **11b**, **13a**, **13b**, **18**, **20**, **22**, **24b**, **26**−**30**, **35**, **36c**, and **37**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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