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# Highly diastereoselective 7-*endo* radical cyclization of ethyl α-methylene-γ-(bromomethyl)dimethylsiloxycarboxylates

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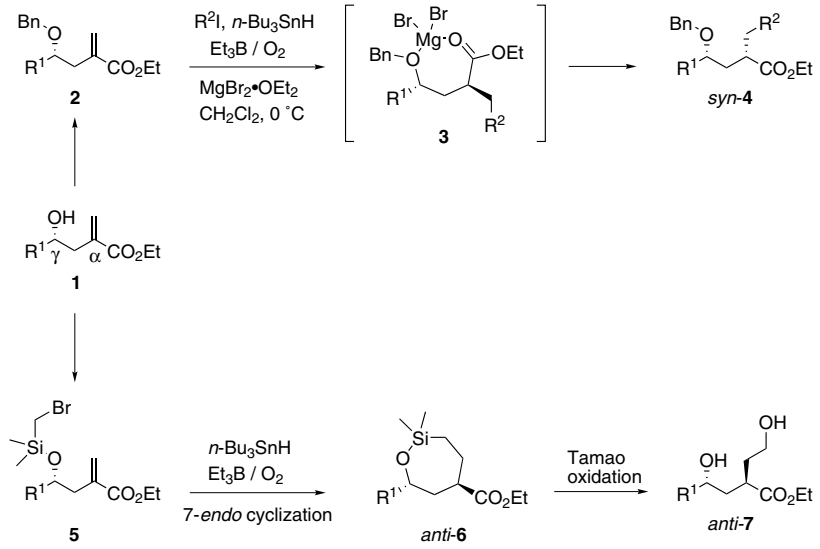
**Abstract**—The 7-*endo* radical cyclization of (bromomethyl)dimethylsilyl ethers derived from ethyl γ-hydroxy-α-methylenecarboxylates bearing a bulky γ-substituent such as isopropyl, cyclohexyl, and *tert*-butyl groups in tetrahydrofuran gave preferentially cyclic silyl ethers bearing the ethoxycarbonyl group *anti* to the γ-substituents in high yields. Treatment of the cyclic silyl ethers with silica gel gave acyclic ethyl γ-hydroxy-α-[2-(hydroxydimethylsilyl)ethyl]carboxylates. The reduction of the cyclization products with DIBAL followed by Tamao oxidation gave the corresponding acyclic triols.


Chelation provides a powerful means of controlling the stereochemistry in acyclic radical reactions.[1,2] Recently, we reported the chelation-controlled 1,3-asymmetric induction in the radical reactions of γ-benzyloxy-α-methylenecarboxylic acid esters **2** with alkyl iodides yielding *syn*-**4** with high diastereoselectivity (Scheme 1).[3,4] The high *syn*-selectivitiy is referred to the H-atom transfer to the outside face of radical center in the sharply folded seven-membered chelate intermediates yielding **3**.[4d,e,5]




**Scheme 1.**

*Keywords*: Radical reaction; α-Silyl radical; Solvent effect; 1,3-Asymmetric induction.
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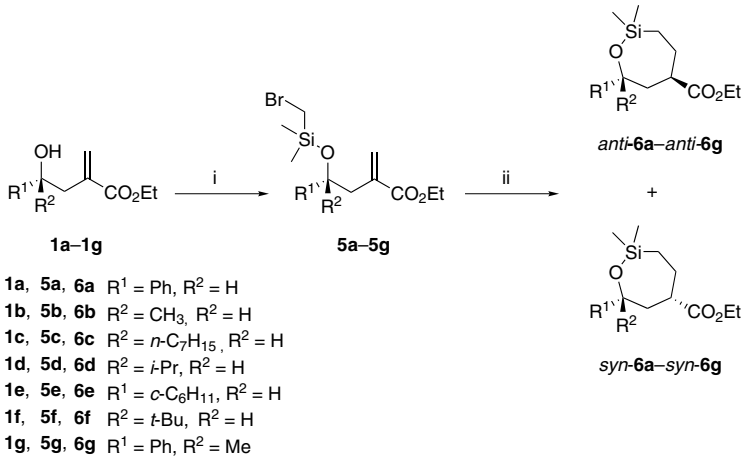



**Scheme 2.** Reagents and conditions: (i) $BrCH_2Si(Me)_2Cl$ (1.3 equiv), DMAP (0.1 equiv), $Et_3N$ (1.1 equiv), $CH_2Cl_2$, 0 °C; (ii) *n*-$Bu_3SnH$ (2 equiv), $Et_3B$ (0.4 equiv), 0 °C.

On the other hand, the 7-*endo* radical cyclization of bromomethylsilyl ethers **5**[6] derived from ethyl γ-hydroxy-α-methylenecarboxylates **1** is expected to give cyclic silyl ethers **6** bearing the ethoxycarbonyl group *anti* to the γ-substituent via the seven-membered radical intermediates (Scheme 1).[7] In contrast to the chelate ring where the carbonyl group is part of the ring, the cyclic radical intermediate possessing an exocyclic ethoxycarbonyl group at the radical center would give rise to the H-atom transfer with *anti* mode. The subsequent cleavage of C–Si bond using Tamao oxidation is therefore expected to give the acyclic dihydroxy esters **7** with *anti* configuration. We report herein the diastereoselectivity in the 7-*endo* radical cyclization of **5** yielding **6** and the subsequent ring cleavage.

The substrates **5a**–**g** were prepared from ethyl γ-hydroxy-α-methylenecarboxylates[4] **1a**–**g** with (bromomethyl)dimethylchlorosilane, respectively (Scheme 2).[6] A summary of the radical cyclizations of **5a**–**g** is shown in Table 1.

**Table 1.** Radical-mediated 7-*endo* cyclization of bromides **5**[a]

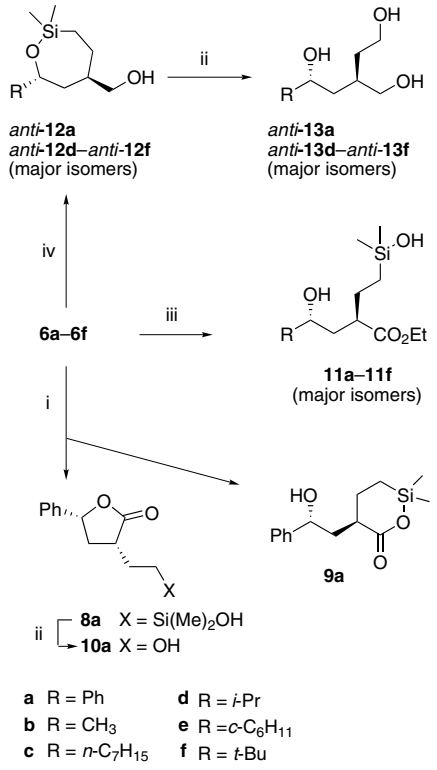
| Entry | Substrate | Solvent | Product | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|---|
| 1 | **5a** | $CH_2Cl_2$ | **6a** | 85 | 1:12 |
| 2 | | $Et_2O$ | | 86 | 1:17 |
| 3 | | 1,4-Dioxane | | 97 | 1:18 |
| 4 | | THF | | 97 | 1:18 |
| 5 | | AcOEt | | 96 | 1:18 |
| 6 | | Hexane | | 96 | 1:12 |
| 7 | | Acetone | | 91 | 1:10 |
| 8 | | MeCN | | 92 | 1:9 |
| 9 | | MeOH | | 93 | 1:10 |
| 10 | **5b** | THF | **6b** | 95 | 1:12 |
| 11 | **5c** | $CH_2Cl_2$ | **6c** | 74 | 1:6.6 |
| 12 | **5d** | THF | **6d** | 90 | 1:34 |
| 13 | **5e** | THF | **6e** | 99 | 1:39 |
| 14 | **5f** | THF | **6f** | 95 | 1:47 |
| 15 | **5g** | THF | **6g** | 88 | 1:2.5 |

[a] Reactions performed with *n*-$Bu_3SnH$ (2 equiv), $Et_3B$ (0.4 equiv) at 0 °C.

Initially, we examined the radical cyclization of **5a** with *n*-$Bu_3SnH$ (2 equiv) and $Et_3B$ (0.4 equiv) at 0 °C in dichloromethane and obtained **6a** in 85% yield with a diastereomer ratio *syn*/*anti* = 1:12 (entry 1). [8] The *anti*-selectivity was not ameliorated at lower temperatures. The use of $Ph_3SnH$ instead of *n*-$Bu_3SnH$ lowered the *anti*-selectivity.[5a] In the reaction of **5a** with tris(trimethylsilyl)silane, a complex mixture was yielded. In diethyl ether, 1,4-dioxane, tetrahydrofuran, or ethyl acetate, **6a** was obtained in high yield and with higher *anti*-selectivity (entries 2–5). However, in nonpolar hexane (entry 6) and in a polar solvent such as acetone, acetonitrile, and methanol (entries 7–9), the *anti*-selectivities were lower.

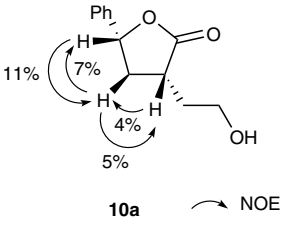
A series of (bromomethyl)dimethylsilyl ethers **5b**–**g** were cyclized in order to probe the effects of substituents $R^1$ and $R^2$ on *syn*–*anti*-selectivity (Table 1). The reactions of **5b** and **5c** bearing a primary alkyl group at the γ-position gave lower *anti*-selectivities (entries 10 and 11). The reaction of **5c** in THF gave a complex mixture. Entries 12–14 show that the cyclization of **5d**–**f** bearing a bulky secondary or tertiary alkyl group at the γ-position gave exclusively *anti*-products **6d**–**f**, respectively. The reaction of **5g** bearing two substituents at the γ-position, however, showed poor diastereoselectivity.

The NOE difference spectra and conformational analysis using CONFLEX calculations[9] of **6a** suggested that the phenyl and ethoxycarbonyl groups are in *anti* relation. Furthermore, the stereochemistry of **6a** was confirmed as follows. Treatment of **6a** with *p*-TsOH in benzene at room temperature gave γ-lactone **8a** in 48% yield together with a mixture containing **9a** (Scheme 3). The NOE experiment of **8a** was not achieved due to the overlapping of signals. The Tamao oxidation of **8a** with hydrogen peroxide gave **10a** in 14% yield. The NOE difference spectra of **10a** showed the phenyl and hydroxyethyl groups are in *syn* relation. Thus, the *anti* stereochemistry of **6a** was established without ambiguity. The configurations of the other products **6b**–**f** were determined by comparing their chemical shift values




**Scheme 3.** Reagents and conditions: (i) *p*-TsOH, benzene, rt; (ii) 30% $H_2O_2$, KF, $KHCO_3$, MeOH–THF (1:1), rt; (iii) silica gel; (iv) DIBAL, $CH_2Cl_2$, −50 °C.

with those of **6a**. The stereochemistry of **6g** was assigned by comparing the chemical shift values of $CH_3$–Si with those of **6a**.




The diastereoselectivity in the radical cyclizations was rationalized based on the conformational analysis of radical intermediate model **A** using CONFLEX and subsequent PM3 calculations.[4d,e] The calculations gave two global minimum energy conformers **A-1** and **A-2** (Fig. 1) and four low energy conformers **A-3**–**A-6** within 1.0 kcal mol$^{-1}$ of the global minimum energy structures. The structures of **A-3**–**A-6** differ from the structure **A-1** or **A-2** only in the geometry of ethoxy group. The H-atom transfer reactions to **A-1**–**A-6** occur on the exposed lower face of radical center to afford the *anti*-selectivity.

To our knowledge, the solvent effect on the conformations associated to the rotation of the polar ethoxycarbonyl group at the prochiral radical center has not been studied.[10] The solvent effects on the diastereomer ratios

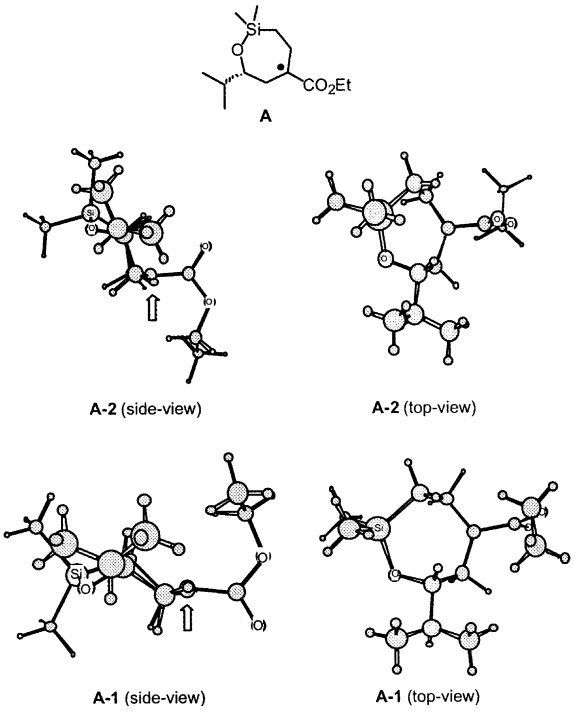



**Figure 1.** Global minimum energy conformers **A-1** and **A-2**.

of **6a** are ascribable to the relative populations of the low energy conformers, each of them exhibiting a different diastereoselectivity. The addition of magnesium dibromide lowered the *anti*-selectivity in the reaction **5a**. The coordination of the Lewis acid to the oxygen atom of ester carbonyl may shield the H-atom transfer.

Finally, the cyclization products **6a**–**f** were allowed to stand on a silica gel column to give the acyclic dihydroxy esters **11a**–**f** in high yields, respectively (Scheme 3).[11] The Tamao oxidation of ester **6a** with hydrogen peroxide gave a complex mixture and the expected product **7a** was not isolated. We, therefore, initially reduced **6a** and **6d**–**f** with diisobutylaluminum hydride (DIBAL) at −50 °C and then oxidized the resulting silyl ethers **12a** and **12d**–**f** with hydrogen peroxide to give triols **13a** and **13d**–**f** in good yields, respectively.[12] The reactions proceeded without epimerization.

In summary we have reported the 7-*endo* cyclization of (bromomethyl)dimethylsilyl ethers **5** yielding preferentially *anti*-**6** and the subsequent ring cleavage yielding dihydroxy esters **11** and triols **13**. The reactions affording *anti*-**13** and the previously reported chelation-controlled radical reaction of γ-benzyloxy-α-methylenecarboxylic acid esters **2** with alkyl iodides yielding *syn*-**4**[4] are complementary to each other with respect to diastereoselectivity.

## References and notes

1. For reviews and books, see: (a) Smadja, W. *Synlett* **1994**, 1–26; (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc.*

*Chem. Res.* **1991**, *24*, 296–304; (c) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145; (d) Renaud, P.; Sibi, M. P. In: *Radicals in Organic Synthesis*; VCH: Weinheim, 2001; Vols. 1–2; (e) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

2. For reviews see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163–171; (b) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562–2579; (c) Guindon, Y.; Guérin, B.; Rancourt, J.; Chabot, C.; Makintosh, N.; Ogilvie, W. W. *Pure Appl. Chem.* **1996**, *68*, 89–96.
3. For a review on 1,3-asymmetric induction, see: (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1224; (b) For radical mediated 1,3-asymmetric inductions via eight-membered chelate rings, see: Hayen, A.; Koch, R.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2758–2761; (c) Hayen, A.; Koch, R.; Saak, W.; Haase, D.; Metzger, J. O. *J. Am. Chem. Soc.* **2000**, *122*, 12458–12468; (d) For recent radical mediated 1,3-asymmetric inductions, see also: Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780–782.
4. (a) Nagano, H.; Toi, S.; Yajima, T. *Synlett* **1999**, 53–54; (b) Nagano, H.; Hirasawa, T.; Yajima, T. *Synlett* **2000**, 1073–1075; (c) Nagano, H.; Matsuda, M.; Yajima, T. *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 174–182; (d) Nagano, H.; Toi, S.; Matsuda, M.; Hirasawa, T.; Hirasawa, S.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2525–2538; (e) Nagano, H.; Ohkouchi, H.; Yajima, T. *Tetrahedron* **2003**, *59*, 3649–3663.
5. (a) Little is known about the conformations of seven-membered cyclic radicals, see Nagano, H.; Mikami, A.; Yajima, T. *Tetrahedron Lett.* **2003**, *44*, 6867–6870; (b) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293–1296; (c) For examples, of five- and six-membered cyclic radicals, see Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–980; (d) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067–4079; (e) Cai, Y.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 467–476.
6. (a) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175–8177; (b) Koreeda, M.; George, I. A. *Chem. Lett.* **1990**, 83–86; (c) Koreeda, M.; Wu, J. *Synlett* **1995**, 850–852; For 6-endo radical cyclization of α-silyl radical, see: (d) Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* **1994**, *35*, 3703–3706; (e) Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098–8100.
7. For a review on intramolecular free radical conjugate additions, see: Zhang, W. *Tetrahedron* **2001**, *57*, 7237–7262.
8. *Typical procedure*: To a solution of **5a** (96 mg, 0.26 mmol) in dry THF (2.6 mL) was added *n*-$Bu_3SnH$ (140 μL, 0.52 mmol) and $Et_3B$ (105 μL, 0.11 mmol) at 0 °C. The mixture was stirred at this temperature for 2 h. KF and water were added and the mixture was stirred at room temperature for 3 h. After filtration through a pad of Florisil, the filtrate was concentrated under reduced pressure. The residue was chromatographed on Florisil (eluent: hexane and then hexane–ethyl acetate (40:1)) to give **6a** (74 mg, 0.25 mmol, 97% yield).
9. (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950–8953; (b) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187–198.
10. For the solvent effects on the stereocontrol of radical reactions, see: (a) Ishihara, T.; Mima, K.; Konno, T.; Yamanaka, H. *Tetrahedron Lett.* **2002**, *43*, 3493–3497; (b) Braslau, R.; Naik, N.; Zipse, H. *J. Am. Chem. Soc.* **2000**, *122*, 8421–8434; (c) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041–11047; (d) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 519–522; (e) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604–8605; (f) Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507–2508; (g) Curran, D. P.; Abraham, A. C. *Tetrahedron* **1993**, *49*, 4821–4840; (h) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457–4470.
11. *Typical procedure*: A solution of the crude cyclization product **6d** prepared from **5d** (88 mg, 0.26 mmol) in hexane was put on a silica gel column and allowed to stand at room temperature for 1 h. Elution with hexane and then with hexane–ethyl acetate (1:1) gave **11d** (60 mg, 83% yield). Yields: **11a** (94%); **11b** (92%); **11c** (conversion yield 91%); **11e** (95%); **11f** (90%).
12. Yields: **12a** (85%); **12d** (95%); **12e** (87%); **12f** (95%); **13a** (80%); **13d** (80%); **13e** (81%); **13f** (conversion yield 87%).